Pathological fracture in a patient with dehydration and hypercalcemia

A 63-year-old African American woman is brought to the emergency room for* **upper arm pain and swelling following a fall at home**. The family has noted that for approximately the past 2 months, the patient has become **progressively fatigued and absentminded**, and she has developed **loss of appetite and weight loss**. She has been **getting up to urinate several times per night** and complains of **thirst**; however, a test for diabetes in her doctor's office was negative. This morning, she lost her balance because she felt "lightheaded" and fell, landing on her left arm. She recently had **frequent respiratory infections.**

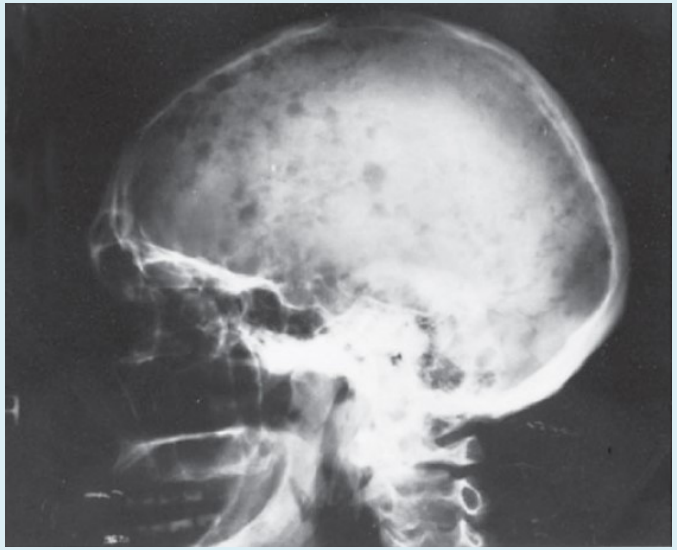
Physical examination is notable for an elderly, thin woman in mild distress as a result of pain. She is afebrile, and her blood pressure is 110/70 mm Hg and heart rate 80 bpm. Her thyroid gland is normal to palpation. **Her mucous membranes are somewhat dry and sticky**. Heart and lung examinations are normal, and carotid auscultation reveals no bruits. Examination of her extremities is significant only for deformity of the left mid-humerus with swelling. The left radial pulse is 2+ and symmetric. The radiologist calls you to confirm the **fracture of the mid-left humerus** but also states that there is the suggestion of some **lytic lesions** of the proximal humerus and recommends a **skull film** (see Figure 36–1). **Serum creatinine level is 2.1 mg/dL**, with normal electrolyte and glucose concentrations, but **serum calcium level is 13 mg/dL** and **hemoglobin level is 9.2 g/dL.**

What is the most likely diagnosis?

What is the most likely underlying etiology in this patient?

What is your next therapeutic step?

What would be the next step regarding diagnosis?



Pathological fracture in a patient with dehydration and hypercalcemia

A 63-year-old African American woman is brought to the emergency room for **upper arm pain and swelling following a fall at home.** The family has noted that for approximately the past 2 months, the patient has become **progressively fatigued and absentminded**, and she has developed **loss of appetite and weight loss**. She has been **getting up to urinate several times per night** and complains of **thirst**; however, a test for diabetes in her doctor's office was negative. This morning, she lost her balance because she felt "lightheaded" and fell, landing on her left arm. She recently had **frequent respiratory infections.**

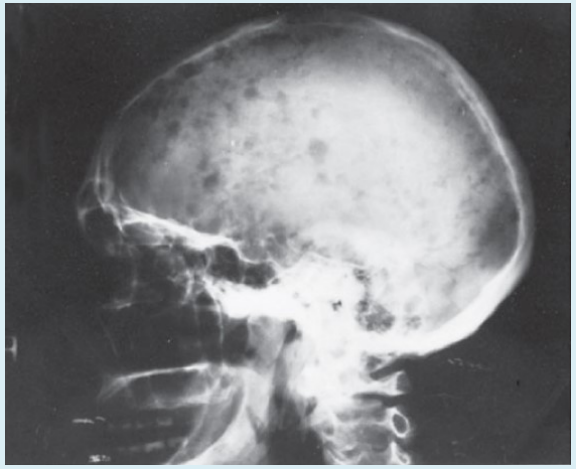
Physical examination is notable for an elderly, thin woman in mild distress as a result of pain. She is afebrile, and her blood pressure is 110/70 mm Hg and heart rate 80 bpm. Her thyroid gland is normal to palpation. **Her mucous membranes are somewhat dry and sticky**. Heart and lung examinations are normal, and carotid auscultation reveals no bruits. Examination of her extremities is significant only for deformity of the left mid-humerus with swelling. The left radial pulse is 2+ and symmetric. The radiologist calls you to confirm the **fracture of the mid-left humerus** but also states that there is the suggestion of some **lytic lesions** of the proximal humerus and recommends a **skull film** (see Figure 36–1). **Serum creatinine level is 2.1 mg/dL**, with normal electrolyte and glucose concentrations, but **serum calcium level is 13 mg/dL** and **hemoglobin level is 9.2 g/dL.**

What is the most likely diagnosis? Hypercalcemia with pathologic fracture of the left humerus.

What is the most likely underlying etiology in this patient? Multiple myeloma.

What is your next therapeutic step? Initial therapy of the hypercalcemia with intravenous (IV) fluids could be started in the emergency room.

What would be the next step regarding diagnosis? Serum and urine electrophoresis would help to identify the presence of a monoclonal gammopathy. Normal serum parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP) levels would exclude other causes of hypercalcemia . Treatment then can be aimed at the underlying cause .



Bony lesions in multiple myeloma. The skull demonstrates the typical "punched out" (*lesioni a stampo*) lesions characteristic of multiple myeloma. The lesion represents a purely **osteolytic lesion** with little or no osteoblastic activity. Bone scintigraphy has a low sensitivity.

Table 36–2 • TREATMENT OF HYPERCALCEMIA

Treatment	Onset	Adverse Effects
Hydration ± loop diuretic	Acute (effect seen in hours)	Volume overload, electrolyte disturbances
Bisphosphonates	Subacute (1-2 d)	Hypophosphatemia, hypomagnesemia, hypocalcemia, osteonecrosis of jaw
Calcitonin	Acute (hours)	Efficacy short-lived (tachyphylaxis)
Glucocorticoids (effective in cancer-induced hypercalcemia)	Lengthy (days)	Hyperglycemia, osteoporosis, immune suppression
Dialysis (renal insufficiency)	Acute (hours)	Volume shifts, electrolyte disorders, complicated procedure

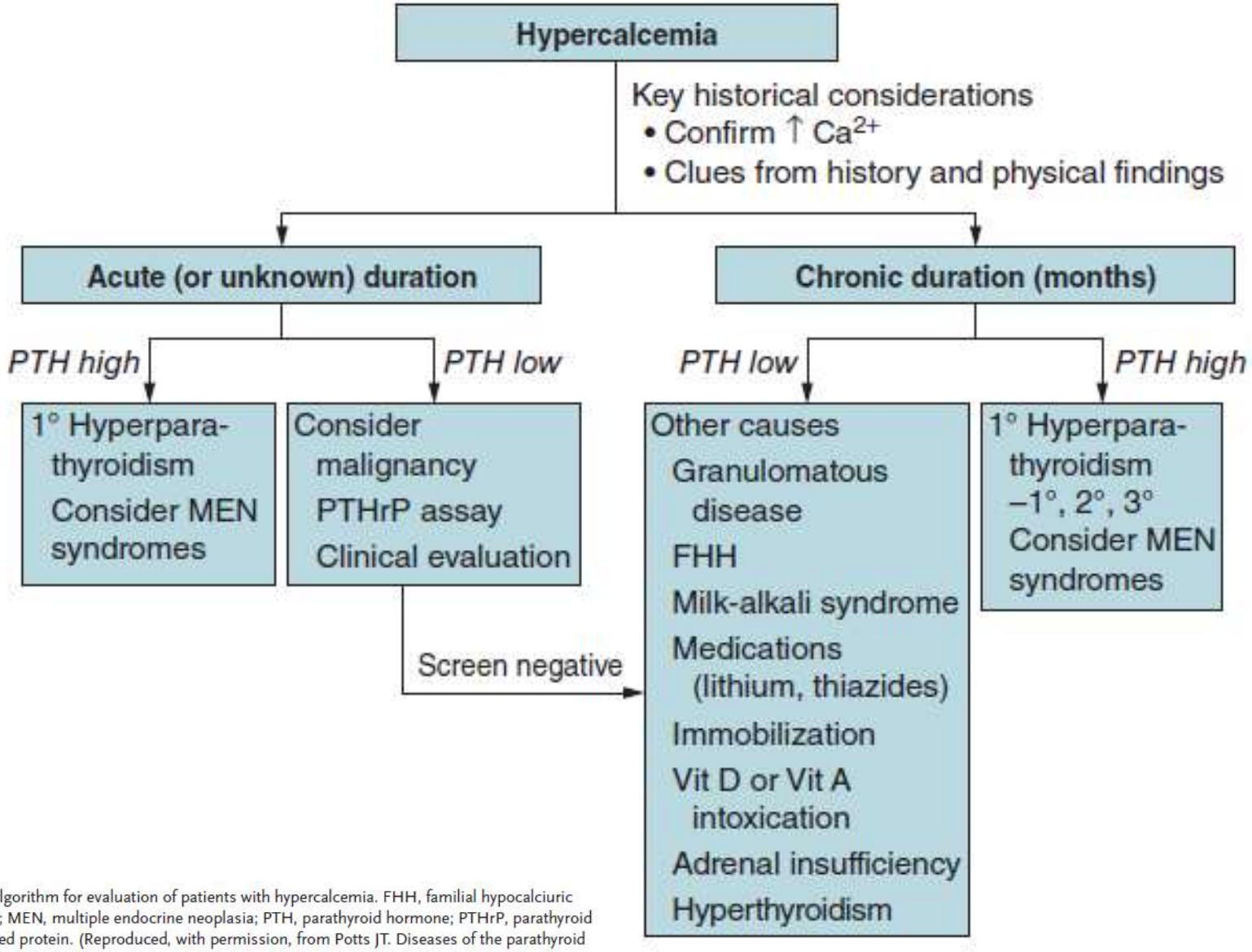


Figure 36–2. Algorithm for evaluation of patients with hypercalcemia. FHH, familial hypocalciuric hypercalcemia; MEN, multiple endocrine neoplasia; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein. (Reproduced, with permission, from Potts JT. Diseases of the parathyroid gland and other hyper- and hypocalcemia disorders. In: Braunwald E, Fauci AS, Kasper DL, et al, eds. *Harrison's Principles of Internal Medicine*. 16th ed. New York, NY: McGraw-Hill; 2005:2260.)

Causes of hypercalcemia

Parathyroid mediated

- Primary hyperparathyroidism (sporadic)
- Inherited variants
- Multiple endocrine neoplasia (MEN) syndromes
- Familial isolated hyperparathyroidism
- Tertiary hyperparathyroidism (renal failure)

Non-parathyroid mediated

- Hypercalcemia of malignancy
- PTHrp
- Osteolytic bone metastases and local cytokines
- Vitamin D intoxication

Chronic granulomatous disorders

- Activation of extrarenal 1 alpha-hydroxylase (increased calcitriol)

Medications: Thiazide diuretics, Lithium

Miscellaneous: Hyperthyroidism, Acromegaly, Immobilization, Parenteral nutrition, Milk alkali syndrome

Table 3
Mechanisms of hypercalcemia of malignancy

Type	Frequency (%)	Bone Metastasis	Causal Agent
Humoral hypercalcemia of malignancy	80	Minimal or absent	PTHrP
Local osteoclastic hypercalcemia	20	Common, extensive	Cytokines, chemokines, PTHrP
$1,25(OH)_2D$-secreting lymphomas	<1	Variable	$1,25(OH)_2D$
Ectopic hyperparathyroidism	<1	Variable	PTH

Abbreviations: $1,25(OH)_2D$, 1,25 hydroxyvitamin D; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related protein.

Table 4
Signs and symptoms of hypercalcemia of malignancy based on system

Neurologic	Muscle weakness, fatigue, hyporeflexia, apathy, disturbances of perception and behavior, lethargy, stupor, and coma
Cardiovascular	Shortened ST segments and QT intervals, widened T waves, bundle branch patterns, depressed ST segments, second-degree block, bradydysrhythmias, complete heart block, cardiac arrest
Gastrointestinal	Nausea, anorexia, vomiting, constipation, ileus, peptic ulcer disease, pancreatitis
Renal	Polyuria, polydipsia, volume depletion, progressive renal insufficiency, nephrocalcinosis, nephrolithiasis
Dermatologic	Pruritus

TABLE 1. Treatment of Hypercalcemia

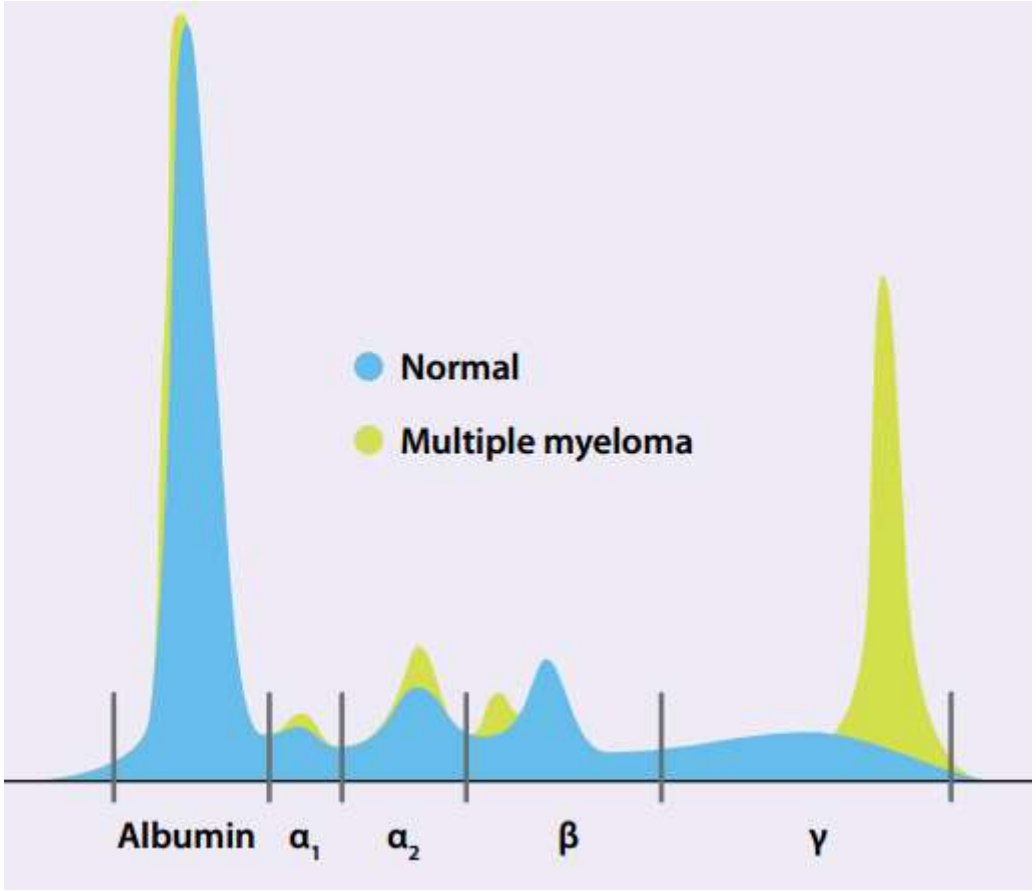
MEDICATION	USUAL DOSE	POINTS TO REMEMBER
Normal saline	Rapid infusion 300-500 cc/h until euvolemic	Use caution in patients with heart failure
Furosemide	20-40 mg iv every 12-24 h	Only after adequate hydration
Pamidronate	60-90 mg iv	Adjust infusion time to creatinine clearance
Zoledronic acid	4 mg iv	Consider alternative treatment in patients with renal failure
Calcitonin	4-8 IU/kg sq or iv every 12 h	Tachyphylaxis occurs quickly
Steroids	Hydrocortisone, 100 mg iv every 6 h or prednisone, 60 mg orally daily	Role usually limited to lymphomas; anticipate hyperglycemia
Mithramycin and gallium		Of historical interest only
Denosumab	Under investigation	Currently approved only for the prevention of skeletal-related events from bone metastases

iv indicates intravenous; sq, subcutaneous.

Paraproteinaemia

Paraproteinaemia denotes presence in the circulation of immunoglobulins produced by a single clone of plasma cells. The paraprotein is recognized as a monoclonal band (M band) on serum electrophoresis.[1] There are 6 major categories:

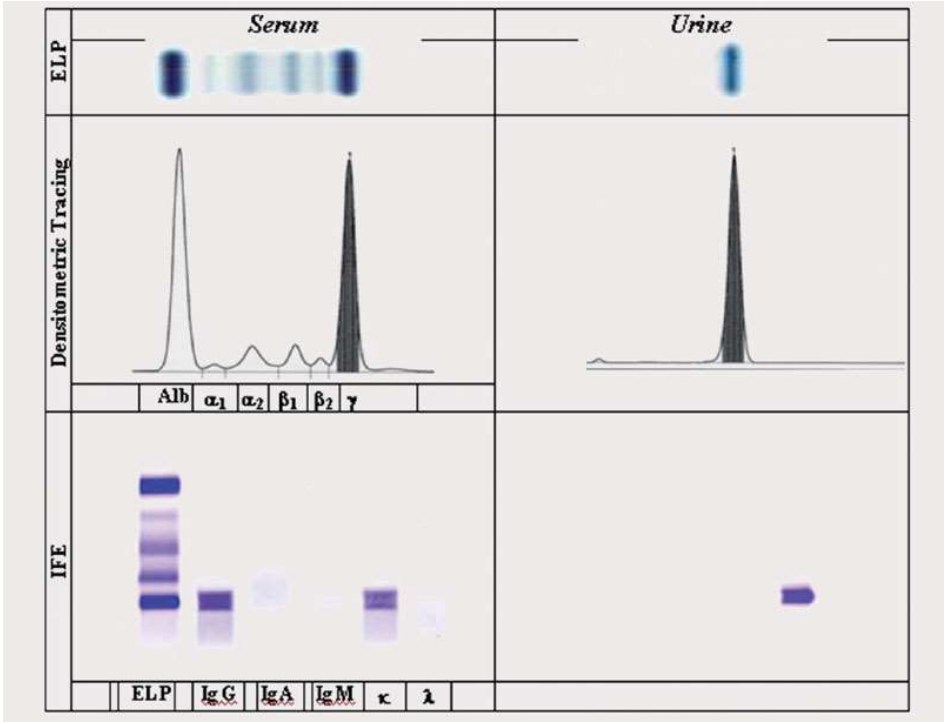
1 Electro*phoresis* and plasma*pheresis* look as though they should share endings, but they do not: Greek *phoros* = *bearing* (*esis* = *process*), but *aphairesis* is Greek for *removal*.



Myeloma: the chief plasma cell dyscrasia (PCD)

PCDs are due to an abnormal proliferation of a single clone of plasma or lymphoplasmacytic cells leading to secretion of immunoglobulin (Ig) or an Ig fragment, causing the dysfunction of many organs (esp kidney).[1] The Ig is seen as a monoclonal band, or paraprotein, on serum or urine electrophoresis (see below).

1 Toxic and inflammatory effects of monoclonal free light chains (FLCs) affect kidney proximal tubule cells; intratubular casts also form via interaction with Tamm-Horsfall proteins.



Blood

Serum protein electrophoresis and immunofixation
Serum immunoglobulins quantitative
Serum free light chain assay

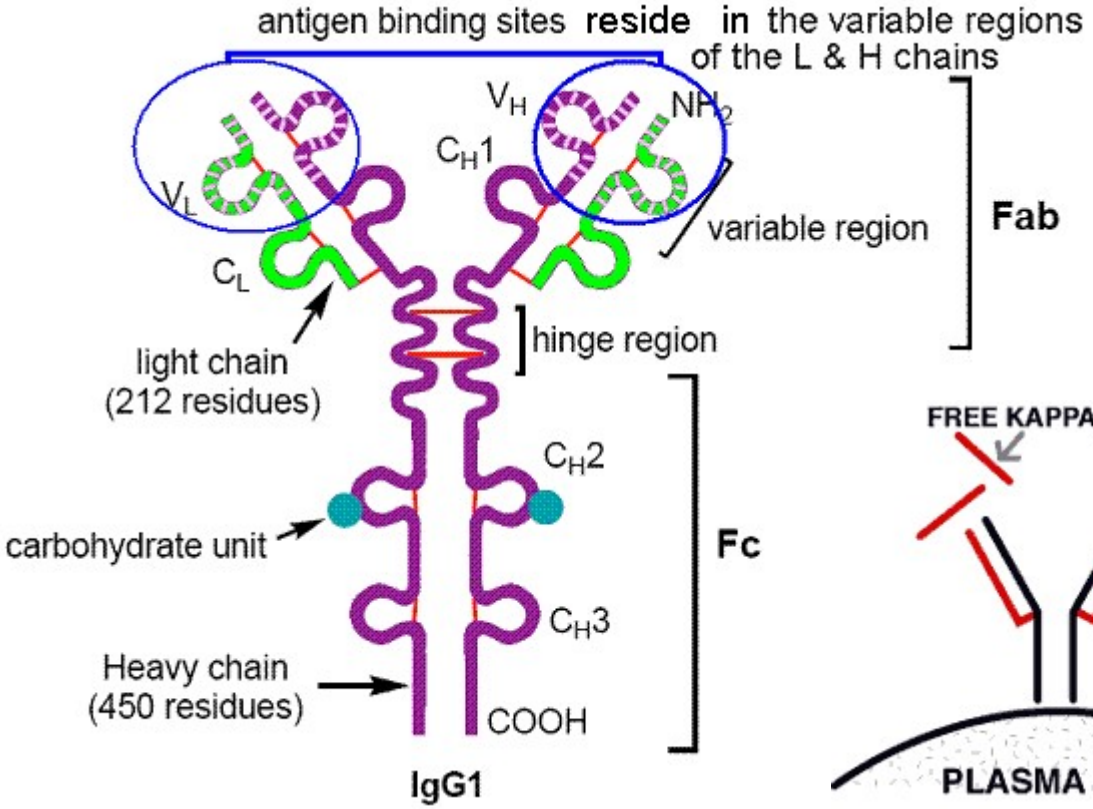
Urine

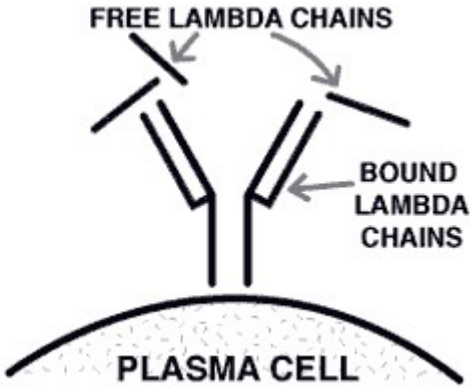
Urine protein electrophoresis and immunofixation
24 h urine for total protein, light chains

Serum and urine protein electrophoresis from a 65-year-old woman with plasma cell myeloma

Classification is based on immunoglobulin (Ig) product—IgG in ~⅔; IgA in ~⅓; A very few are IgM or IgD. Other Ig levels are low ('immunoparesis', causing ↑susceptibility to infection). In ~⅔, urine contains Bence Jones proteins, which are free Ig light chains of kappa (κ) or lambda (λ) type, filtered by the kidney.

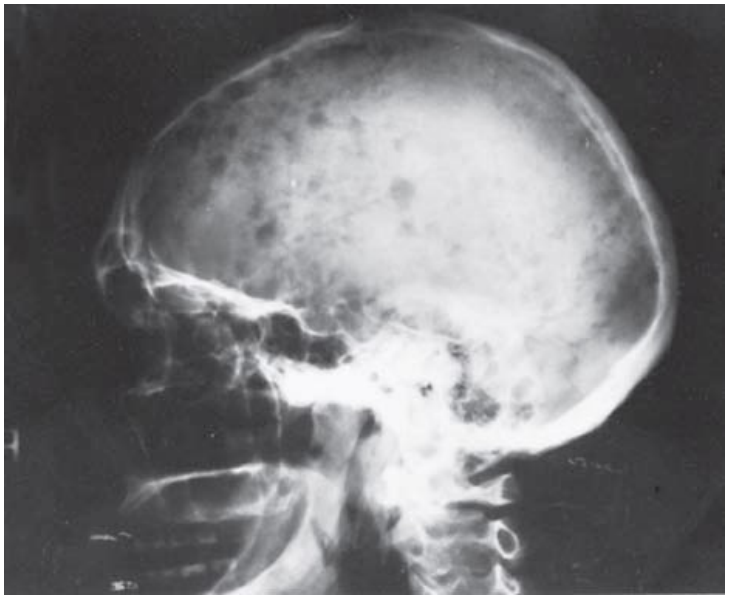
Incidence 5/100,000. Peak age: 70yrs. ♂:♀≈1. Afro-Caribbeans:Caucasians≈2:1.





Symptoms ►Do serum protein electrophoresis & ESR on all over 50 with back pain

- *Osteolytic bone lesions* causing backache, pathological fractures (eg long bones or ribs) and vertebral collapse. *Hypercalcaemia* may be symptomatic (p690). Lesions are due to osteoclast activation, from signalling by myeloma cells.



Bony lesions in multiple myeloma. The skull demonstrates the typical "punched out" (*lesioni a stampo*) lesions characteristic of multiple myeloma. The lesion represents a purely **osteolytic lesion** with little or no osteoblastic activity. Bone scintigraphy has a low sensitivity.

Bone scintigraphy ^{99m}Tc labelled bisphosphonates are readily taken up by bone, and concentrate in areas of pathology (tumours, metastases, fractures) (fig 3).

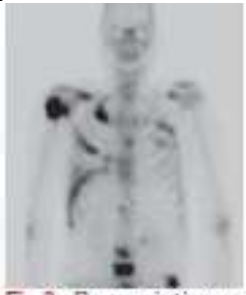


Fig 3. Bone scintigram showing metastases.

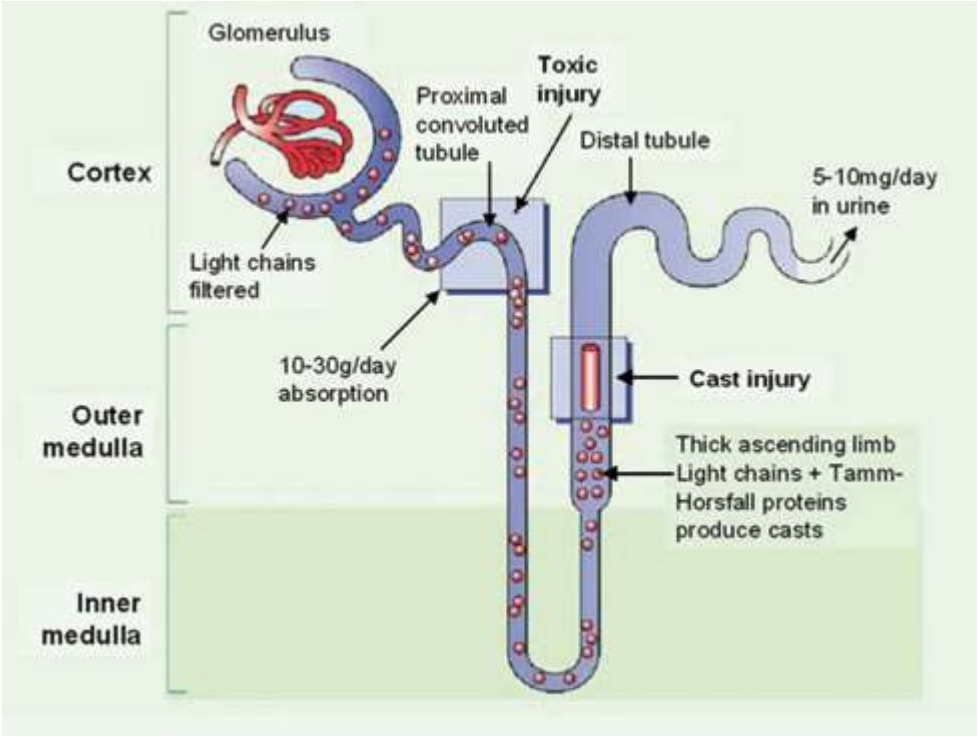
Symptoms ►Do serum protein electrophoresis & ESR on all over 50 with back pain.

- *Osteolytic bone lesions* causing backache, pathological fractures (eg long bones or ribs) and vertebral collapse. *Hypercalcaemia* may be symptomatic (p690). Lesions are due to osteoclast activation, from signalling by myeloma cells.
- *Anaemia, neutropenia, or thrombocytopenia* may result from marrow infiltration by plasma cells, leading to symptoms of anaemia, infection and bleeding.
- *Recurrent bacterial infections* due to immunoparesis, and also because of neutropenia due to the disease and from chemotherapy.
- *Renal impairment* due to light chain deposition (p314 & p364) seen in up to 20% at diagnosis—mainly caused by precipitation of light chains with the Tamm-Horsfall protein in the distal loop of Henle.[113] Also, monoclonal immunoglobulins induce changes in glomeruli. A rare type of damage is deposits of light chains in the form of AL-amyloid and subsequent nephrosis[114] (and other systemic problems, p364).

The **Tamm–Horsfall mucoprotein** , also known as uromodulin, is the most abundant protein excreted in ordinary urine. Uromodulin is secreted by renal tubular cells. It is the matrix of urinary casts and contributes to formation of calcium-containing kidney stones.

Myeloma (p362) is characterized by excess production of monoclonal antibody ± light chains, which are excreted and detected in ⅔ of cases as Bence Jones proteinuria. Myeloma kidney is due to blockage of tubules by casts, consisting of light chains. The light chains have a direct toxic effect on tubular cells, causing acute tubular necrosis. *Features:* AKI, CKD, amyloidosis (may cause proteinuria and nephrotic syndrome), hypercalcaemic nephropathy. *Treatment:* Ensure fluid intake of 3L/day to prevent further impairment. Dialysis may be required in AKI. It might be possible to remove light chains by plasma exchange using special filters.

myeloma kidney or myeloma cast nephropathy



International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

Lancet Oncol 2014; 15: e538–48

Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

PET-CT=^{18}F-fluorodeoxyglucose PET with CT. *Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.

Tests FBC—normocytic normochromic anaemia, film—rouleaux formation (p322), persistently ↑ESR or PV (p366), ↑urea and creatinine, ↑Ca^{2+} (in ~40%), alk phos usually ↔ unless healing fracture. Marrow *et al*—figs 1-4. *Screening test:* Serum and urine electrophoresis. β_2-microglobulin (as a prognostic test). *Imaging:* X-rays: lytic 'punched-out' lesions, eg pepper-pot skull, vertebral collapse, fractures or osteoporosis. CT or MRI may be useful to detect lesions not seen on XR. *Diagnostic criteria:* BOX.

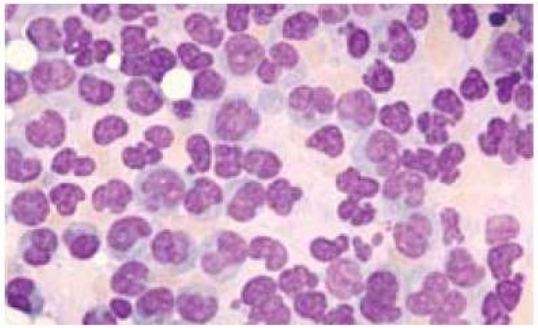


Fig 1. Myeloma bone marrow: many plasma cells with abnormal forms.

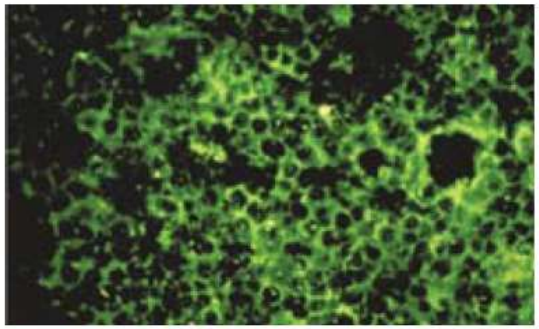


Fig 2. Marrow section in myeloma, stained with IgG kappa monoclonal antibody.

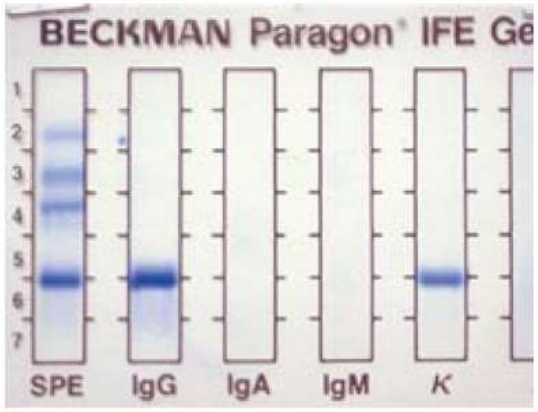


Fig 3. An IgG kappa paraprotein monoclonal band (immunofixation electrophoresis; a control sample has run on the left).

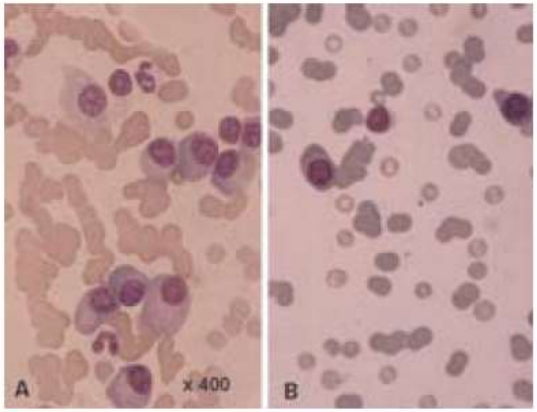


Fig 4. Plasma cells in myeloma. A: marrow smear, B: peripheral smear. Note rouleaux formation of red cells (p322 & p362).

Myeloma diagnosis

Have a high index of suspicion, ►eg in bone pain or back pain which is not improving, do an ESR and film and electrophoresis. Diagnostic criteria:

1. Monoclonal protein band in serum or urine electrophoresis
2. Plasma cells ↑ on marrow biopsy
3. Evidence of end-organ damage from myeloma:
   - Hypercalcaemia
   - Renal insufficiency
   - Anaemia
4. Bone lesions: a skeletal survey after diagnosis detects bone disease: X-rays of chest; all of spine; skull; pelvis ± Tc-99m MIBI and PET (p754)

MGUS is present in 1% of all adults, (3% of those over age 50 years and more than 5% in those over age 70 years). Thus, among all patients with paraproteins, MGUS is far more common than multiple myeloma. MGUS is defined as bone marrow monoclonal plasma cells < 10% in the setting of a paraprotein (serum M-protein < 3 g/dL [< 30 g/L]) and the absence of end-organ damage. In approximately one-quarter of cases, MGUS progresses to overt malignant disease in a median of one decade. The transformation of MGUS to multiple myeloma is approximately 1% per year. Smoldering multiple myeloma is defined as a serum M-protein > 3 g/dL (> 30 g/L) or bone marrow monoclonal plasma cells ≥ 10% in the absence of end-organ damage. Multiple myeloma, smoldering multiple myeloma, and MGUS must be distinguished from reactive (benign) polyclonal hypergammaglobulinemia (which is commonly seen in cirrhosis).

	Test
Blood	Serum protein electrophoresis and immunofixation Serum immunoglobulins quantitative Serum free light chain assay Total serum protein, serum albumin, creatinine, calcium, electrolytes, lactate dehydrogenase, β2-microglobulin Haemoglobin, white blood cell count, differential count, platelet count
Urine	Urine protein electrophoresis and immunofixation 24 h urine for total protein, light chains
Bone marrow	Aspirate and biopsy for plasma cell count, morphology, amyloid* Cytogenetic evaluation and fluorescence in-situ hybridisation for the detection of del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q+
Bones	Skeletal survey (conventional x-ray) or low-dose CT scan without contrast
Whole body	MRI*, PET-CT* Tissue biopsy for solitary or extraosseous plasmacytoma*

*Useful under some circumstances.

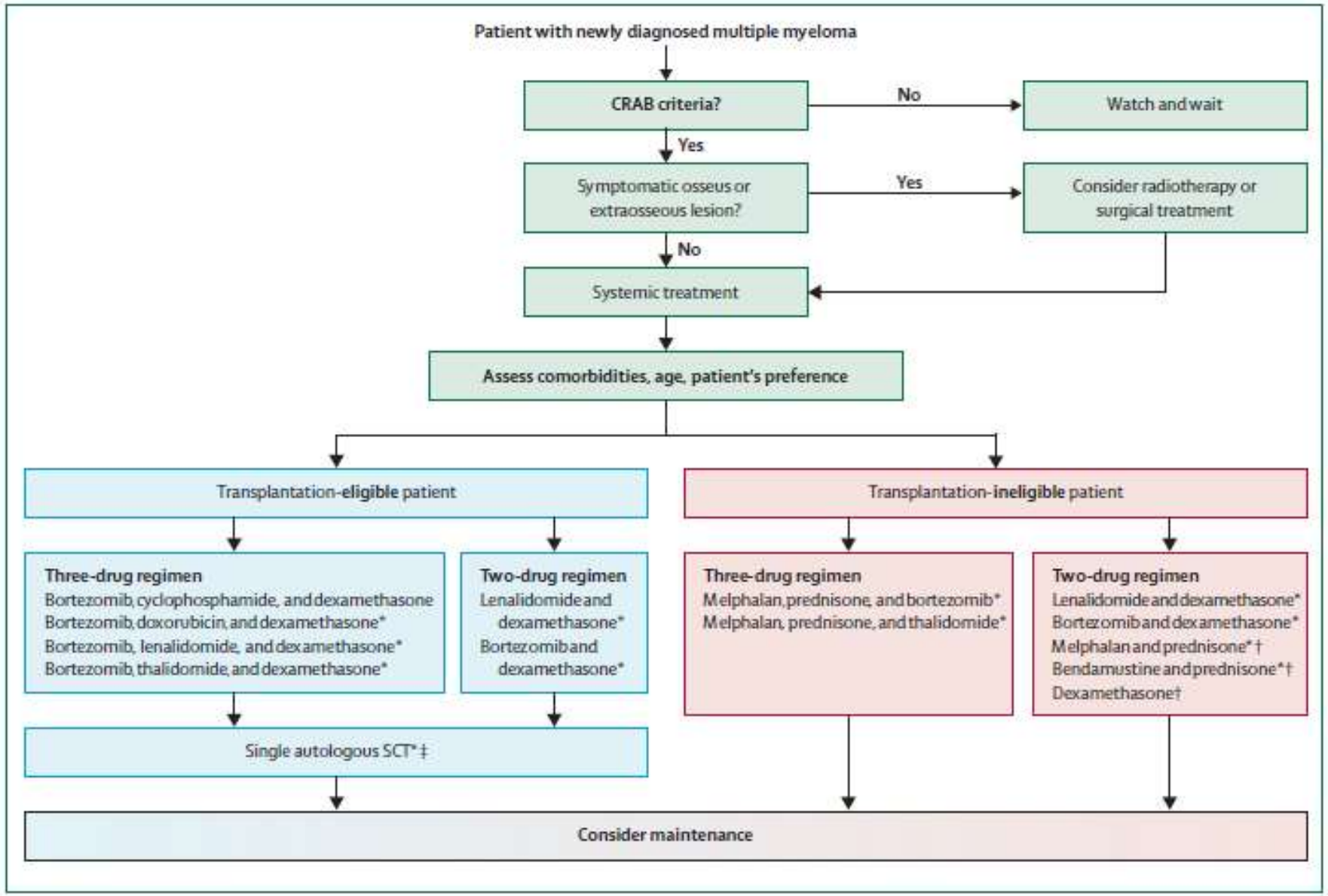
Table 1: **Diagnostic workup for multiple myeloma**

Lancet 2015; 385: 2197–208

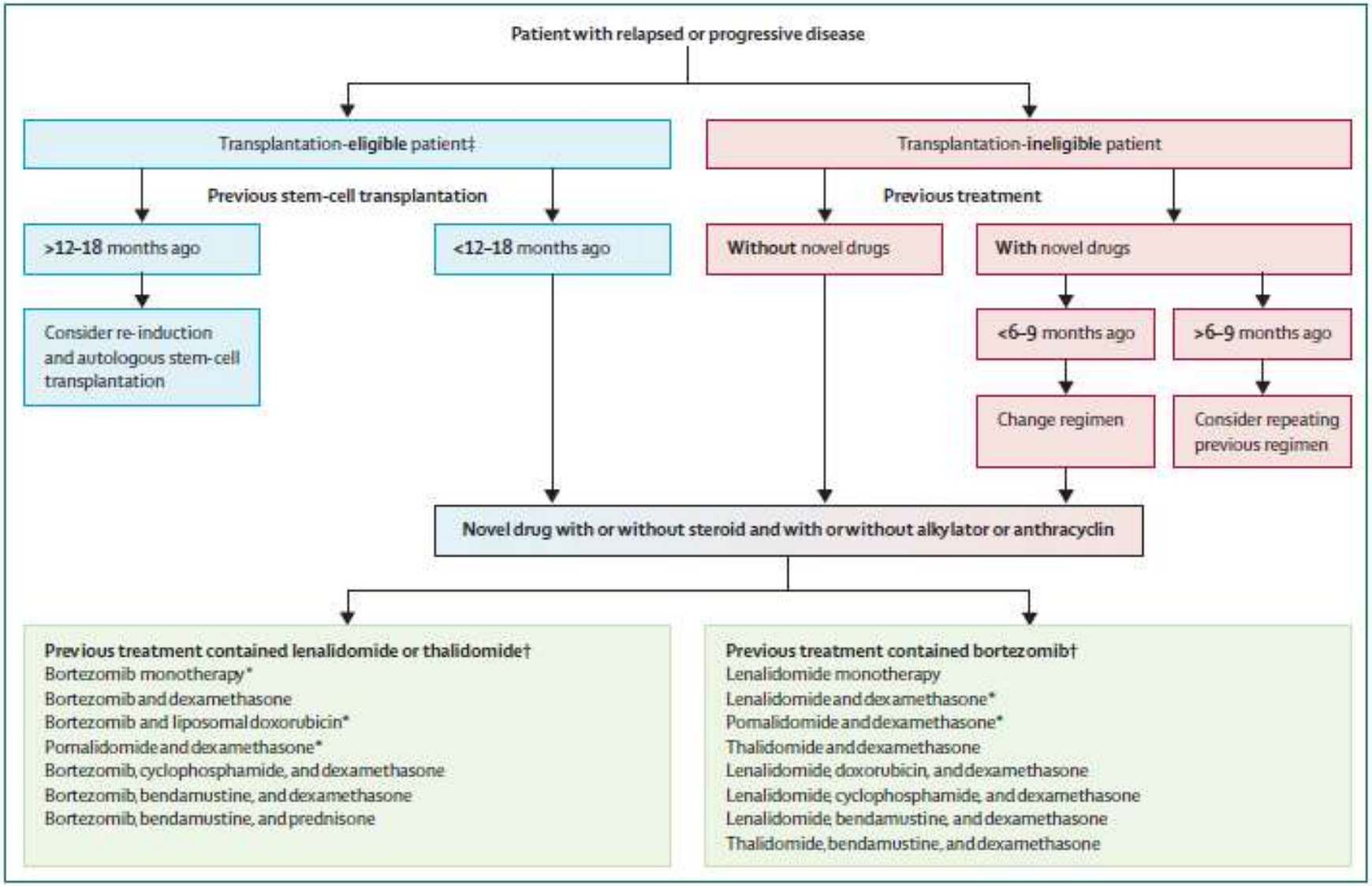
Treatment[115] *Supportive:* • Bone pain should be treated with analgesia (avoid NSAIDs due to risk of renal impairment). Give all patients a *bisphosphonate* (clodronate, zolendronate or pamidronate), as they reduce fracture rates and bone pain. Local radiotherapy can help rapidly in focal disease. Orthopaedic procedures (vertebroplasty or kyphoplasty) may be helpful in vertebral collapse. • Anaemia should be corrected with *transfusion*, and *erythropoietin* may be used. • Renal failure: rehydrate, and ensure adequate fluid intake of 3L/day to prevent further renal impairment by light chains. Dialysis may be needed in acute renal failure • Infections: Treat rapidly with broad-spectrum antibiotics until culture results are known. Regular IV *immunoglobulin infusions* may be needed if recurrent.

Chemotherapy: If unsuitable for intensive Rx, *melphalan + prednisolone* is used. This can control disease for ~1yr, reducing paraprotein levels and bone lesions. Adding *bortezomib* increases the time to relapse.[116] In due course, disease may become uncontrollable and resist treatment. Adding *thalidomide* (a teratogenic immunomodulator) improves event-free survival, eg in the elderly.[117] SE: birth defects; drowsiness; neuropathy; neutropenia; sepsis; orthostatic hypotension; thromboembolism (aspirin, or full anticoagulation is probably wise if risk ↑, eg hyperviscosity, or other comorbidities).[118] In fitter people, a more vigorous approach is used (high-dose therapy and stem-cell rescue, HDT) with a **VAD** type regimen: *Vincristine*, *Adriamycin* and *Dexamethasone*. Autologous stem cell transplant may then be done, which improves survival but is not curative. Allogeneic transplantation can be curative in younger patients, but carries ↑risk of mortality (~30%). Thalidomide or bortezomib may be tried in relapsed disease. NB: *lenalidomide* is similar to thalidomide and, being a bit more potent, may have a role,[119] as may *bendamustine* (it drives cell death by promoting mitotic catastrophe in melphalan-resistant myeloma cells).[120]

Prognosis Worse if: >2 osteolytic lesions, β_2-microglobulin >5.5mg/L, Hb <11g/L; albumin <30g/L.[121] Cause of death: infection; renal failure (transplants have a role).[122]



Lancet 2015; 385: 2197–208



Lancet 2015; 385: 2197–208

Complications of myeloma

- *Hypercalcaemia* (p690). This occurs with active disease, eg at presentation or relapse. Rehydrate vigorously with IV saline 0.9% 4–6L/d (careful fluid balance). IV bisphosphonates, eg zolendronate or pamidronate, are useful for treating hypercalcaemia acutely.
- *Spinal cord compression* (p470). Occurs in 5% of those with myeloma. Urgent MRI if suspected. Treatment is with dexamethasone 8–16mg/24h PO and local radiotherapy.
- *Hyperviscosity* (p366) causes reduced cognition, disturbed vision, and bleeding. It is treated with plasmapheresis to remove light chains.
- *Acute renal injury* is treated with rehydration. Urgent dialysis may be needed.

Hyperviscosity syndrome

Blood is made to move! Our beautiful images seem to deny this, as if haematology were just a branch of histology. So what are the intrinsic disorders of flow? If blood viscosity rises there may be a few telltale signs before the quick becomes dead, eg lethargy; confusion; cognition↓; CNS disturbance; chest pain; abdominal pain; faints; visual disturbance (eg vision↓, amaurosis fugax, retinopathy—eg engorged retinal veins, haemorrhages, exudates; and a blurred disc as seen in fig 1a). The visual symptoms ('slow-flow retinopathy') are like 'looking through a watery car windscreen' (fig 1b). Other causes of slow-flow retinopathy: carotid disease and Takayasu's disease (p726). Also hyperviscosity may cause spontaneous GI or GU bleeding.

Fig 1a & 1b. Hyperviscosity syndrome.

Causes of high blood viscosity: Very high red cell count (haematocrit >50, eg polycythaemia rubra vera), white cell count (>100×10^9/L, eg leukaemia), or plasma components—usually immunoglobulins, in myeloma or Waldenström's macroglobulinaemia (p364, as IgM is larger and so ↑ viscosity more than the same amount of IgG). Drugs: oral contraceptives, diuretics, IV Ig, erythropoietin, chemotherapy, radio-contrast media.

Treatment: Urgent treatment is needed which depends on the cause. Venesection is done in polycythaemia. Leukopheresis in leukaemias to remove white cells. Plasmapheresis in myeloma and Waldenström's: blood is withdrawn via a plasma exchange machine, the supernatant plasma from this is discarded, and the RBCs returned to the patient after being resuspended in a suitable medium.

INFECTIONS IN THE IMMUNOCOMPROMISED PATIENT

ESSENTIALS OF DIAGNOSIS

- Fever and other symptoms may be blunted because of immunosuppression.
- A contaminating organism in an immunocompetent individual may be a pathogen in an immunocompromised one.
- The interval since transplantation and the degree of immunosuppression can narrow the differential diagnosis.
- Empiric broad-spectrum antibiotics may be appropriate in high-risk patients whether or not symptoms are localized.

- Immunocompromised patients have defects in their natural defense mechanisms resulting in an increased risk for infection.
- infection is often severe, rapidly progressive, and life threatening.
- Organisms that are not usually problematic in the immunocompetent person may be important pathogens in the compromised patient (eg, *Staphylococcus epidermidis, Corynebacterium jeikeium, Propionibacterium acnes, Bacillus species).*
- *Therefore, culture* results must be interpreted with caution, and isolates should not be disregarded as merely contaminants.

A. Impaired Humoral Immunity (hypogammaglobulinemia)

- Congenital
- Acquired (multiple myeloma, chronic lymphocytic leukemia, splenectomy).

Patients with ineffective humoral immunity lack opsonizing antibodies and are at particular risk for infection with encapsulated organisms, such as *Haemophilus influenzae, Neisseria meningitides,* and *Streptococcus pneumoniae. Although rituximab is normally* thought of as being linked to impaired cellular immunity, it has been associated with the development of *Pneumocystis jirovecii infection as well as with hepatitis B* reactivation.

B. Granulocytopenia (Neutropenia)

hematopoietic cell transplantation, myelosuppressive chemotherapy, acute leukemias.

Infection risk→ granulocyte <1000/mcL, (great risk<100/mcL)

The granulocytopenic patient is particularly susceptible to infections with gram-negative enteric organisms, *Pseudomonas*, *gram-positive cocci* (particularly *Staphylococcus aureus, S epidermidis, and viridans*streptococci), *Candida, Aspergillus, and other fungi* that have recently emerged as pathogens such as *Trichosporon, Scedosporium, Fusarium, and the mucormycoses.*

C. Impaired Cellular Immunity

HIV infection; lymphoreticular malignancies (Hodgkin disease); immunosuppressive medications (prolonged high-dose corticosteroid treatment, cyclosporine, tacrolimus, and other cytotoxic drugs as in patients receiving therapy for organ transplantation or solid tumors- Tumor necrosis factor (TNF) inhibitors (etanercept and infliximab).

Patients with cellular immune dysfunction are susceptible to infections by a large number of organisms, particularly ones that replicate intracellularly. Examples include bacteria, such as Listeria, Legionella, Salmonella, and Mycobacterium; viruses, such as herpes simplex, varicella,
and CMV; fungi, such as Cryptococcus, Coccidioides, Histoplasma, and Pneumocystis; and protozoa, such as Toxoplasma. **Patients taking TNF inhibitors have specific defects that increase risk of bacterial, mycobacterial (particularly tuberculosis), and fungal infections (primary
and reactivation)**.

D. Hematopoietic Cell Transplant Recipients

E. Solid Organ Transplant Recipients

F. Other Immunocompromised States

A large group of patients who are not specifically immunodeficient are at increased risk for infection due to:

debilitating injury (eg, burns or severe trauma), invasive procedures (eg, chronic central intravenous catheters, Foley catheters, dialysis catheters), central nervous system dysfunction (which predisposes patients to aspiration pneumonia and decubitus ulcers), obstructing lesions (eg, pneumonia due to an obstructed bronchus, pyelonephritis due to nephrolithiasis, cholangitis secondary to cholelithiasis), use of broadspectrum antibiotics.

Diabetes mellitus (alterations in cellular immunity, resulting in mucormycosis, emphysematous pyelonephritis, and foot infections).

►►Prevention

There is great interest in preventing infection with **prophylactic antimicrobial regimens** but no uniformity of opinion about optimal drugs or dosage regimens.

Hand washing is the simplest and most effective means of decreasing hospital associated
infections, especially in the compromised patient.

Invasive devices such as **central and peripheral lines and Foley catheters** are potential sources of infection.

Colony stimulating factors decrease rates of infection and episodes of febrile neutropenia, but not mortality, during chemotherapy or during stem-cell transplantation.

Amyloidosis[11]

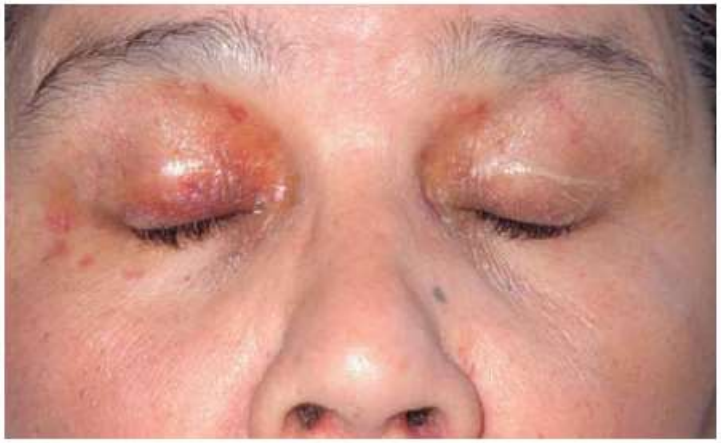
Amyloid...the amorphous fibrillar protein

This is a group of disorders characterized by extracellular deposits of a protein in abnormal fibrillar form, resistant to degradation. The following are the systemic forms of amyloidosis. Amyloid deposition is also a feature of Alzheimer's disease, type 2 diabetes mellitus and haemodialysis-related amyloidosis.

AL amyloid (primary amyloidosis) Proliferation of plasma cell clone → amyloidogenic monoclonal immunoglobulins → Fibrillar light chain protein deposition → Organ failure → Death. Associations: myeloma (15%); Waldenström's, lymphoma. Organs involved:

- Kidneys: glomerular lesions—proteinuria and nephrotic syndrome
- Heart: restrictive cardiomyopathy (looks 'sparkling' on echo), arrhythmias, angina
- Nerves: peripheral and autonomic neuropathy; carpal tunnel syndrome
- Gut: macroglossia (big tongue), malabsorption/weight↓, perforation, haemorrhage, obstruction, and hepatomegaly
- Vascular: purpura, especially periorbital—a characteristic feature (fig 1).

℞: Optimize nutrition; oral melphalan + prednisolone extends median survival from 13 months following diagnosis to 17 months.[124] High-dose IV melphalan with autologous peripheral blood stem cell transplantation may be better.



Periorbital purpura in amyloidosis.

AA amyloid (secondary amyloidosis) Here amyloid is derived from serum amyloid A, an acute phase protein, reflecting chronic inflammation in rheumatoid arthritis, UC/Crohn's, familial Mediterranean fever, and chronic infections—TB, bronchiectasis, osteomyelitis. It affects kidneys, liver, and spleen (fig 2), and may present with proteinuria, nephrotic syndrome or hepatosplenomegaly. Macroglossia is not seen; cardiac involvement is rare.[2] ℞: manage the underlying condition optimally.

2 Murmurs; low voltage ECG, ventricular hypertrophy, diastolic dysfunction.[125]

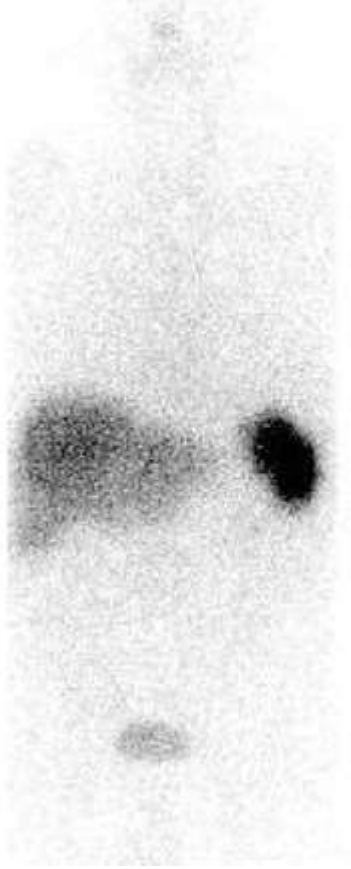


Fig 2. Areas of amyloid deposition in liver and spleen in amyloidosis (isotope scan). ©BMJ/BUP.

Familial amyloidosis (autosomal dominant, eg from mutations in transthyretin, a transport protein produced by the liver). Usually causes a sensory or autonomic neuropathy ± renal or cardiac involvement. Liver transplant can cure.

Diagnosis is made with biopsy of affected tissue, and positive Congo Red staining with red-green birefringence under polarized light microscopy. The rectum or subcutaneous fat are relatively non-invasive sites for biopsy and are +ve in 80%.

Prognosis Median survival is 1–2 years. Patients with myeloma and amyloidosis have a shorter survival than those with myeloma alone.

Paraproteinaemia

There are 6 major categories:

1 *Multiple myeloma:* See p362.
2 *Waldenström's macroglobulinaemia:* This is a lymphoplasmacytoid lymphoma producing a monoclonal IgM paraprotein. Hyperviscosity is common (p366), with CNS and ocular symptoms. Lymphadenopathy and splenomegaly are also seen. ↑ESR, with IgM paraprotein on serum electrophoresis. *Rx:* None if asymptomatic. Chlorambucil, fludarabine or combination chemotherapy may be used. Plasmapheresis[1] for hyperviscosity (p366).
3 *Primary amyloidosis:* See below.
4 *Monoclonal gammopathy of uncertain significance* (MGUS) is common (3% >70yrs). There is a paraprotein in the serum but no myeloma, 1° amyloid, macroglobulinaemia or lymphoma, with no bone lesions, no Bence Jones protein and a low concentration of paraprotein, with <10% plasma cells in the marrow. Some develop myeloma or lymphoma. Refer to a haematologist (?for marrow biopsy).[123]
5 *Paraproteinaemia in lymphoma or leukaemia:* Eg seen in 5% of CLL.
6 *Heavy chain disease:* This is where neoplastic cells produce free Ig heavy chains. α chain disease is the most important, causing malabsorption from infiltration of small bowel wall. It may progress to lymphoma.

36.1 On routine blood work performed for a life insurance application, a 48-year-old premenopausal woman was found to have a calcium level of 12 mg/dL (normal = 8.8-10.4 mg/dL) and a phosphate level of 2 mg/dL (normal = 3.0-4.5 mg/dL). She is not anemic and has no symptoms. Her medical history is significant for osteoporosis, discovered on a dual-energy x-ray absorptiometry (DEXA) scan performed last year. Which of the following is the most likely cause of her hypercalcemia?

A. Multiple myeloma
B. Parathyroid adenoma
C. Familial hypocalciuric hypercalcemia
D. Sarcoidosis
E. Undiagnosed breast cancer

36.2 A 62-year-old asymptomatic woman is noted to have multiple myeloma and hypercalcemia, but no bone lesions or end-organ damage. Which of the following therapies is useful for immediate treatment of the hypercalcemia?

A. Bisphosphonates.
B. Erythropoietin.
C. Dexamethasone plus thalidomide.
D. Interferon-α.
E. Observe without treatment since she is asymptomatic.

36.3 A 22-year-old African American woman presents with worsening cough and shortness of breath over 6 weeks, which did not improve with a course of antibiotics or antitussives. Her serum calcium level is found to be 12.5 mg/dL, and a chest x-ray reveals bilateral hilar lymphadenopathy. She has erythema nodosum on her legs. Which of the following is the most likely diagnosis?

A. Sarcoidosis
B. Mycoplasma pneumonia
C. Acute lymphoblastic leukemia
D. Squamous cell carcinoma of the lung
E. Pulmonary embolism

36.4 A 66-year-old man with known metastatic squamous cell carcinoma of the esophagus is brought to the emergency room for increasing lethargy and confusion. He is clinically dehydrated, his serum calcium level is 14 mg/dL, and his creatinine level is 2.5 mg/dL but 1 month ago was 0.9 mg/dL. Which therapy for his hypercalcemia should be instituted first?

A. Intravenous bisphosphonate
B. Intravenous furosemide
C. Glucocorticoids
D. Intravenous normal saline
E. Chemotherapy for squamous cell carcinoma

36.1 **B.** An asymptomatic, most likely chronically elevated calcium level is most likely caused by primary hyperparathyroidism due to a parathyroid adenoma. The hypercalcemia is presumed to be chronic because she has osteoporosis and is premenopausal.

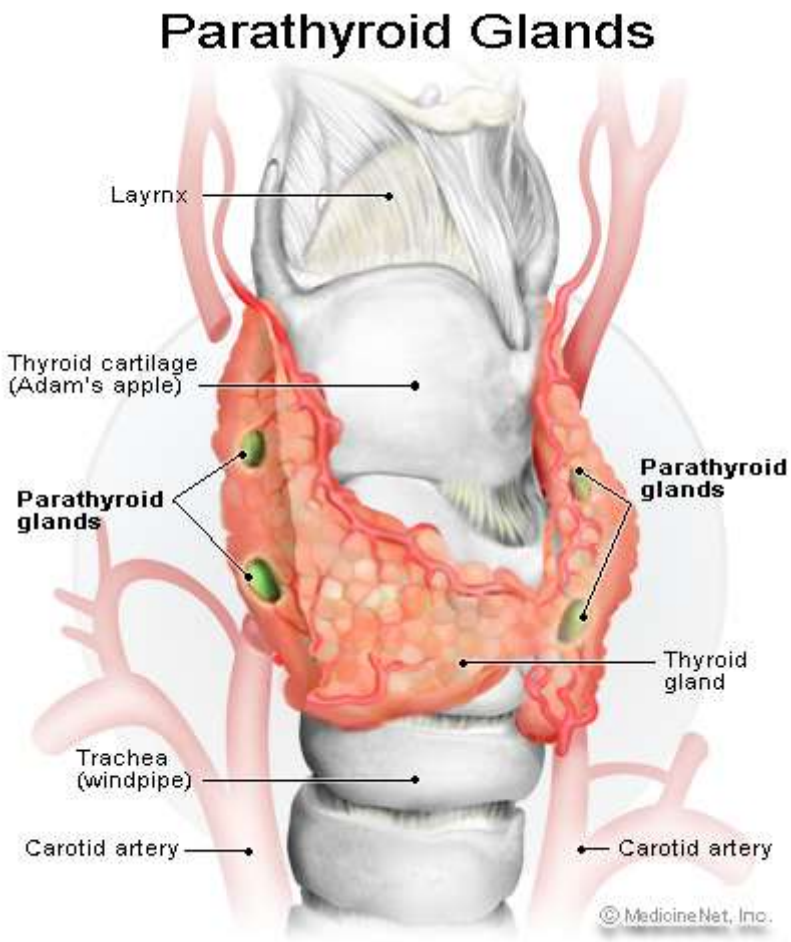
36.2 **A.** Bisphosphonates are helpful in controlling hypercalcemia through inhibition of osteoclastic bone reabsorption. Dexamethasone, in combination with thalidomide, is useful in treatment of the myeloma, with a slower effect on the calcium level.

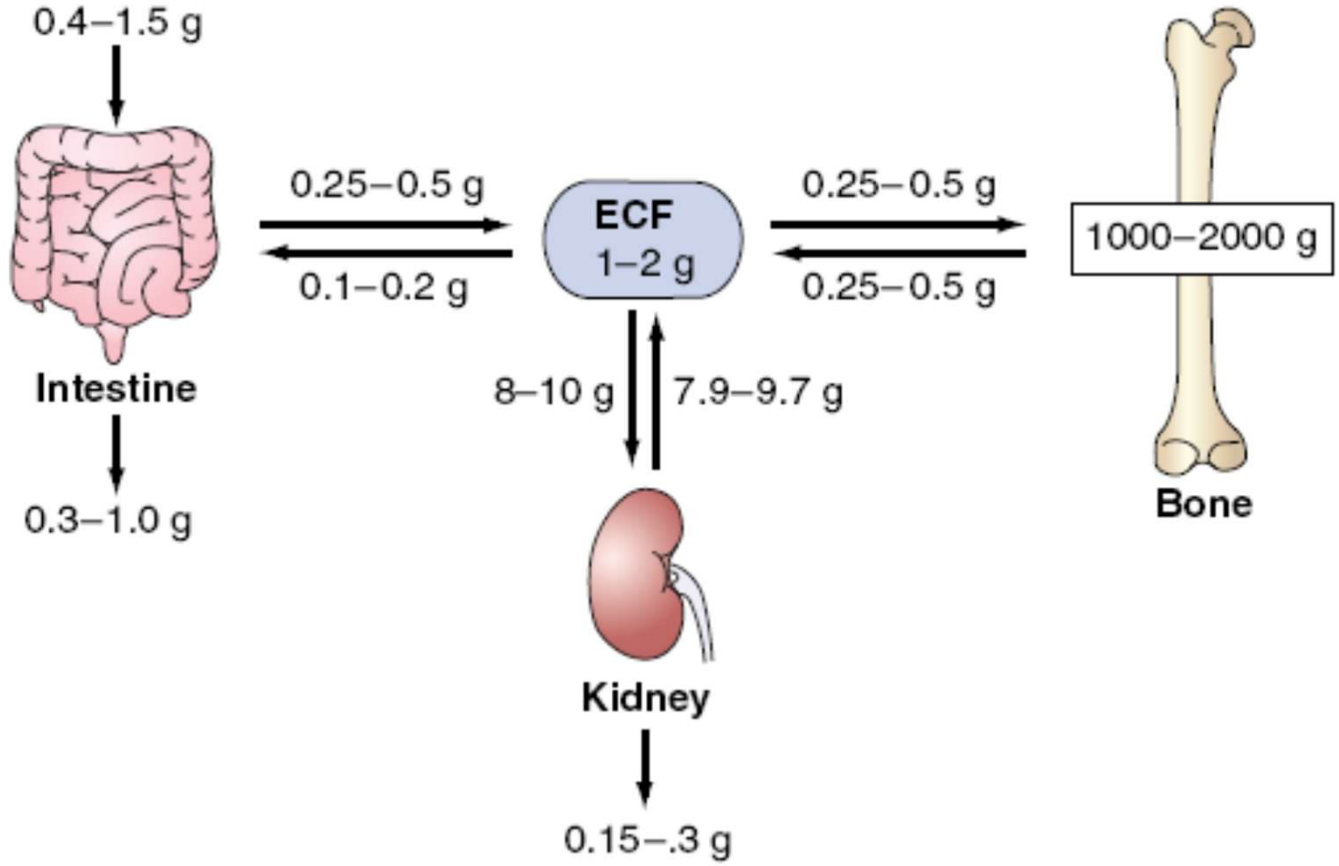
36.3 **A.** Both sarcoidosis and lymphoma can present with cough, dyspnea, and hilar adenopathy on chest x-ray. In approximately 10% of cases, sarcoidosis can cause elevated calcium levels through the production of 1,25-vitamin D that occurs in the macrophages of the granulomas. This can also be seen in granulomas caused by tuberculosis and in lymphoma. Leukemia usually does not present in this manner, although it can cause hypercalcemia. Squamous cell carcinoma of the lung would be unusual in a patient of this age, and the radiographic presentation is atypical.

36.4 **D.** Although all of the other therapies listed may be helpful in the treatment of hypercalcemia, given the clinical findings of dehydration and elevated creatinine level with a history of previously normal renal function, volume expansion with normal saline would correct the dehydration and presumed prerenal azotemia, allowing the kidneys to more efficiently excrete calcium. Other therapies can be added if the response to normal saline alone is insufficient.

Le molecole delle Immunoglobuline (gli anticorpi) sono proteine composte da due catene peptidiche "pesanti" identiche unite a due catene "leggere" identiche.
Esistono cinque tipi diversi di catene pesanti (che determinano la classe dell'immunoglobulina, IgG, IgA, IgM, IgE, IgD) ma solo due tipi di catene leggere, k (kappa) e λ (lambda).
La capacità di riconoscere e legare l'antigene è dovuta alla parte terminale (regione variabile) sia delle catene pesanti che di quelle leggere. Normalmente una piccola quantità di catene leggere in eccesso rispetto alle pesanti viene prodotta dai linfociti del sistema immunitario: queste catene che non si combinano a formare immunoglobuline complete vengono rilasciate nel sangue e lasciate passare in piccola quantità dai reni nelle urine.
L'aumento di concentrazione nel sangue delle catene leggere k o λ può essere di due tipi: policlonale o monoclonale. Policlonalità significa che le catene leggere presenti sono quelle prodotte da tutti gli insiemi (cloni) di linfociti che producono tutto il repertorio di anticorpi, meccanismo di difesa specifico dell'organismo. Un aumento di catene leggere policlonali può essere dovuto a un danno renale, che ne diminuisce la capacità di metabolizzarle ed eliminarle: entrambi i tipi k e λ aumentano, perciò il loro rapporto rimane invariato. Invece, un aumento di concentrazione di catene leggere monoclonali deriva da un eccesso di produzione di catene di un solo tipo ad opera di un unico clone di linfociti, che prolifera oltre i suoi limiti normali (come nel caso del mieloma multiplo, della macroglobulinemia di Waldestroem, ecc.).
Tradizionalmente, le patologie delle plasmacellule vengono diagnosticate usando l' elettroforesi delle proteine sieriche e urinarie (SPEP/UPEP), seguita dall' immunofissazione sierica (IFE) per determinare quale tipo di immunoglobulina sia presente in eccesso. Può essere prescritto anche un esame del sangue per misurare la concentrazione delle immunoglobuline intatte (IgG, IgM, IgA).

Class and Molecular Weight (daltons)	Structure	Percent of Total Serum Immunoglobulin (Half-life in serum)	Properties and Functions
IgM 970,000	 Pentamer	5%–13% (10 days)	First antibody produced during the primary immune response. Only class produced in response to T-independent antigens. Provides direct protection by neutralizing viruses and toxins, immobilizing motile organisms, preventing the adherence of microbes to cell surfaces, and agglutinating/precipitating antigens. Binding of IgM to antigen leads to activation of the complement system (classical pathway).
IgG 146,000	 Monomer	80%–85% (21 days)	Most abundant class in the blood and tissue fluids. Provides longest term protection because of its long half-life. Transported across the placenta, providing protection to a developing fetus; long half-life extends the protection through the first several months after birth. Provides direct protection by neutralizing viruses and toxins, immobilizing motile organisms, preventing the adherence of microbes to cell surfaces, and agglutinating/precipitating antigens. Binding of IgG to antigen facilitates phagocytosis, leads to activation of the complement system (classical pathway) and elicits antibody-dependent cellular cytotoxicity.
IgA monomer 160,000; secretory IgA 390,000	 Dimer in secretions	10%–13% (6 days)	Most abundant class produced, but the majority is secreted into mucus, tears, and saliva, providing mucosal immunity. Also found in breast milk, protecting the intestinal tract of breast-fed infants. Protects mucous membranes by neutralizing viruses and toxins, immobilizing motile organisms and preventing attachment of microbes to cell surfaces.
IgD 184,000	 Monomer	< 1% (3 days)	Involved in the development and maturation of the antibody response. Functions in serum have not been clearly described.
IgE 188,000	 Monomer	< 0.01% (2 days)	Binds via the Fc region to mast cells and basophils; this bound IgE allows those cells to detect parasites and other antigens and respond by releasing their granule contents. Involved in many allergic reactions.


Parathyroid Glands
Layrnx
Thyroid cartilage
(Adam's apple)
Parathyroid
glands
Parathyroid
glands
Thyroid
gland
Trachea
(windpipe)
Carotid artery
Carotid artery
© MedicineNet, Inc.



Calcium homeostasis. Schematic illustration of calcium content of extracellular fluid (ECF) and bone as well as of diet and feces; magnitude of calcium flux per day as calculated by various methods is shown at sites of transport in intestine, kidney, and bone. Ranges of values shown are approximate and chosen to illustrate certain points discussed in text. In conditions of calcium balance, rates of calcium release from and uptake into bone are equal.

METABOLISMO DEL CALCIO – assorbimento

> nei segmenti prossimali del tenue (per trasporto attivo)

< nei " distali del tenue (assorbimento per diffusione)

Viene assorbito circa il 20 - 40% del calcio ingerito con la dieta il resto è eliminato con le feci.

METABOLISMO DEL CALCIO – eliminazione

Escrezione renale media = 100-400 mg/die

In realtà calcio filtrato dal glomerulo = 6-10g/die

→ 60% riassorbito dal tubulo prossimale

→ 25% " dall'ansa di Henle

→ >10% dal tubulo distale

↑

Modulato dal PTH

La secrezione nel lume intestinale è fissa e indipendente dall'assorbimento.

PARATORMONE (PTH)

Prodotto dalle ghiandole paratiroidi (emivita 2-5 minuti).

Mantiene stabile la concentrazione di calcio nel liquido extracellulare.

L'ipocalcemia causa ipersecrezione PTH, il quale determina:

1) ↑ dissoluzione della fase minerale dell'osso = passaggio di Ca dall'osso al sangue
2) ↑ riassorbimento tubulare renale di Ca
3) potenzia l'assorbimento intestinale di Ca, tramite l'attivazione della vitamina D

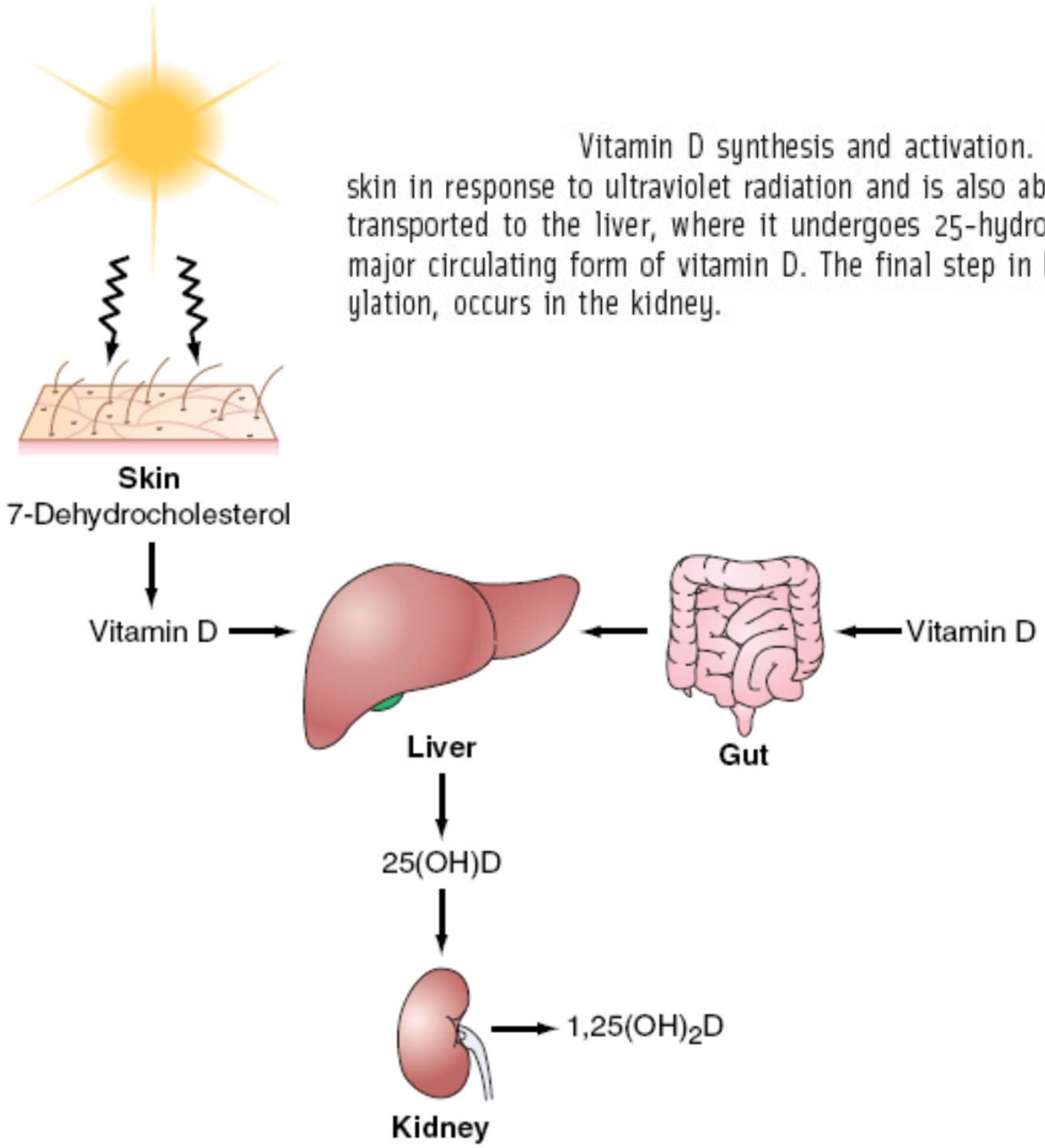
NB = l'effetto sull'osso non è solo di mobilizzazione del Ca, ma di *rimodellamento* e azione anabolizzante (in particolare la stimolazione cronica sugli osteoblasti).

VITAMINA D

Organi conivolti nella sintesi del metabolita attivo 1,25 didrossivitamina D = cute, fegato, rene.

L'ipocalcemia, attraverso la secrezione di PTH, causa iperattivazione di vitamina D, la quale determina:

1) ↑ assorbimento intestinale di Ca
2) ↑ passaggio di Ca dall'osso al sangue (in modo sinergico al PTH)



Vitamin D synthesis and activation. Vitamin D is synthesized in the skin in response to ultraviolet radiation and is also absorbed from the diet. It is then transported to the liver, where it undergoes 25-hydroxylation. This metabolite is the major circulating form of vitamin D. The final step in hormone activation, 1α-hydroxylation, occurs in the kidney.

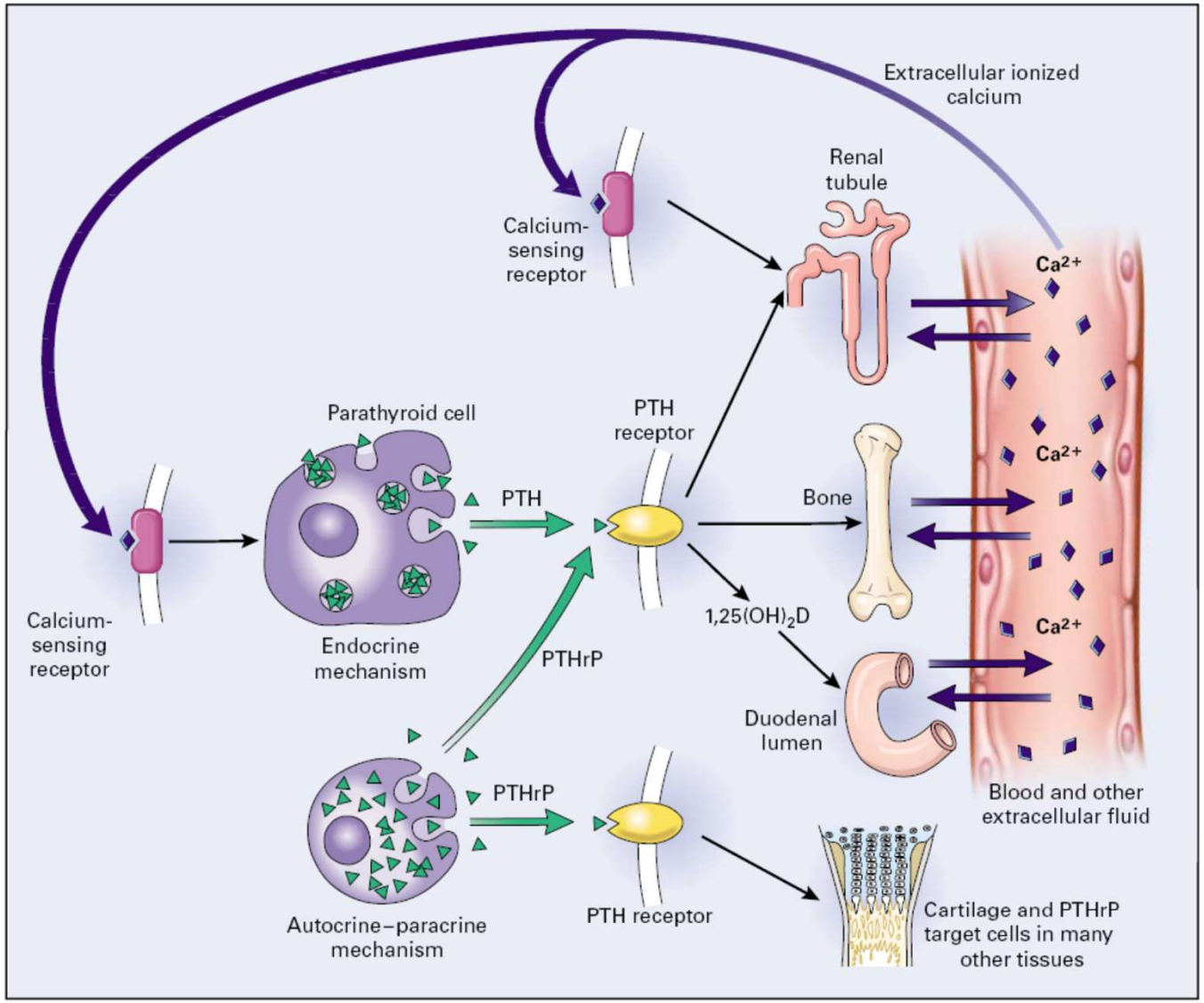
CALCITONINA

Prodotto dalle cellule C della ghiandola tiroide.

L'ipercalcemia causa ipersecrezione di calcitonina, la quale determina:

1) inibizione degli osteoclasti e del riassorbimento osseo

2) ↑ clereance renale di Ca



. The Parathyroid Axis.

The synthesis of parathyroid hormone (PTH) and parathyroid hormone–related peptide (PTHrP) is shown on the left, and their target sites of action are shown on the right. Both act by means of the same receptor (also termed the type 1 PTH receptor). Negative feedback of 1,25-dihydroxyvitamin D is not shown. See the text for further descriptions. An excess or deficiency of parathyroid hormone may be treated either at the level of parathyroid hormone release (and the parathyroid hormone receptors) or at selected sites distal to the parathyroid hormone receptors. Blue arrows indicate extracellular calcium flow.

ipercalcemia

TABLE 332-1 Classification of Causes of Hypercalcemia

I. Parathyroid-related
   A. Primary hyperparathyroidism
      1. Solitary adenomas
      2. Multiple endocrine neoplasia

II. Malignancy-related
   A. Solid tumor with metastases (breast)
   B. Solid tumor with humoral mediation of hypercalcemia (lung, kidney)
   C. Hematologic malignancies (multiple myeloma, lymphoma, leukemia)

III. Vitamin D–related
   A. Vitamin D intoxication
   B. ↑ $1,25(OH)_2D$; sarcoidosis and other granulomatous diseases

Macrophages obtained from granulomatous tissue convert 25(OH)D to 1,25(OH)2D at an increased rate.

IV. Associated with high bone turnover
   A. Hyperthyroidism
   B. Immobilization
   C. Thiazides

Types of Hypercalcemia Associated with Cancer.

Type	Frequency (%)	Bone Metastases	Causal Agent	Typical Tumors
Local osteolytic hypercalcemia	20	Common, extensive	Cytokines, chemokines, PTHrP	Breast cancer, multiple myeloma, lymphoma
Humoral hypercalcemia of malignancy	80	Minimal or absent	PTHrP	Squamous-cell cancer, (e.g., of head and neck, esophagus, cervix, or lung), renal cancer, ovarian cancer, endometrial cancer, HTLV-associated lymphoma, breast cancer
$1,25(OH)_2D$-secreting lymphomas	<1	Variable	$1,25(OH)_2D$	Lymphoma (all types)
Ectopic hyperparathyroidism	<1	Variable	PTH	Variable

PTH denotes parathyroid hormone, PTHrP PTH-related protein, $1,25(OH)_2D$ 1,25-dihydroxyvitamin D, and HTLV human T-cell lymphotrophic virus.

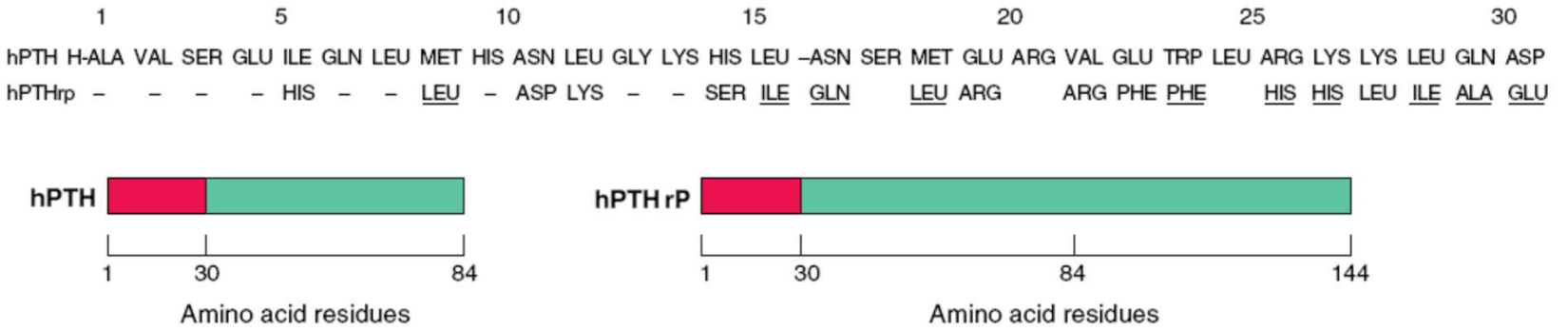
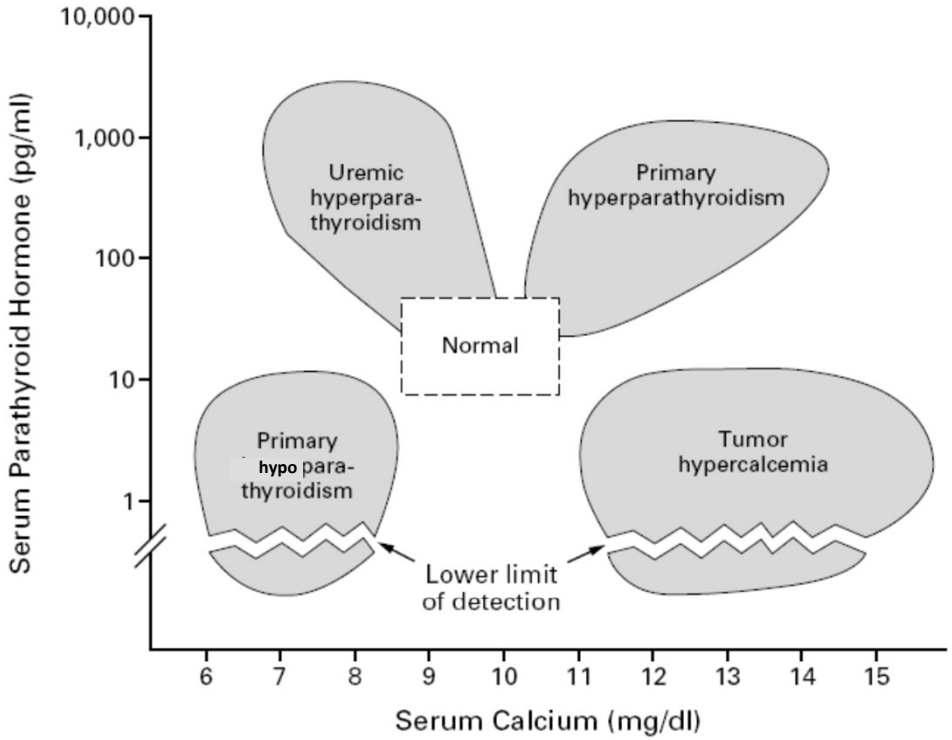
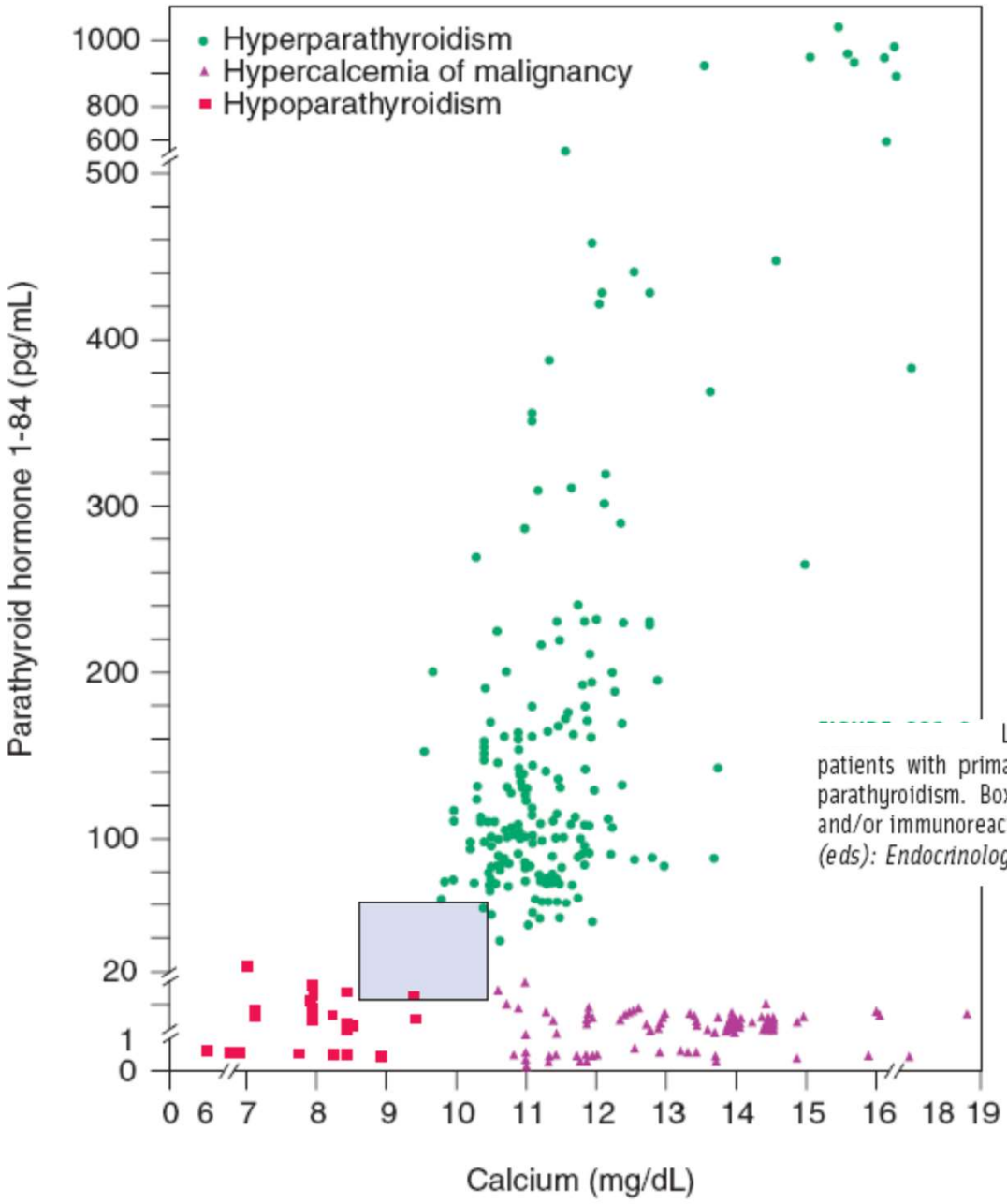


FIGURE 332-1 Schematic diagram to illustrate similarities and differences in structure of human parathyroid hormone (PTH) and human PTH-related peptide (PTHrP). Close structural (and functional) homology exists between the first 30 amino acids of hPTH and hPTHrP. The PTHrP sequence may be ≥144 amino acid residues in length. PTH is only 84 residues long; after residue 30, there is little structural homology between the two. Dashed lines in the PTHrP sequence indicate identity; underlined residues, although different from those of PTH, still represent conservative changes (charge or polarity preserved). Eleven amino acids are identical, and a total of 21 of 30 are homologues.



Serum Calcium and Parathyroid Hormone Concentrations in Patients with Hypercalcemia and Hypocalcemia Due to Various Causes.

The diagnosis of a serious mineral disorder is usually clear, as illustrated by the nonoverlapping domains in the figure, but in the early stages of these disorders, the values for either serum calcium or parathyroid hormone may overlap with the normal ranges. The following diagnoses are not shown: familial hypocalciuric hypercalcemia (midpoint of the range for serum calcium, 11.5 mg per deciliter, and for serum parathyroid hormone, 30 pg per milliliter); neonatal severe primary hyperparathyroidism (midpoint for serum calcium, 18 mg per deciliter, and for serum parathyroid hormone, 500 pg per milliliter); hypercalciuric hypocalcemia (midpoint for serum calcium, 7 mg per deciliter, and for serum parathyroid hormone, 10 pg per milliliter); tertiary uremic hyperparathyroidism (midpoint for serum calcium, 11 mg per deciliter, and for serum parathyroid hormone, 2000 pg per milliliter); tertiary hyperparathyroidism after renal transplantation that corrected uremia (midpoint for serum calcium, 12 mg per deciliter, and for serum parathyroid hormone, 200 pg per milliliter); and adynamic bone disease with uremia (midpoint for serum calcium, 9 mg per deciliter, and for serum parathyroid hormone, 50 pg per milliliter). To convert values for serum calcium to millimoles per liter, multiply by 0.25, and to convert values for serum parathyroid hormone to picomoles per liter, multiply by 0.11.



Levels of immunoreactive parathyroid hormone (PTH) detected in patients with primary hyperparathyroidism, hypercalcemia of malignancy, and hypoparathyroidism. Boxed area represents the upper and normal limits of blood calcium and/or immunoreactive PTH. [*From SR Nussbaum, JT Potts, Jr, in L DeGroot, JL Jameson (eds): Endocrinology, 4th ed. Philadelphia, Saunders, 2001, with permission.*]

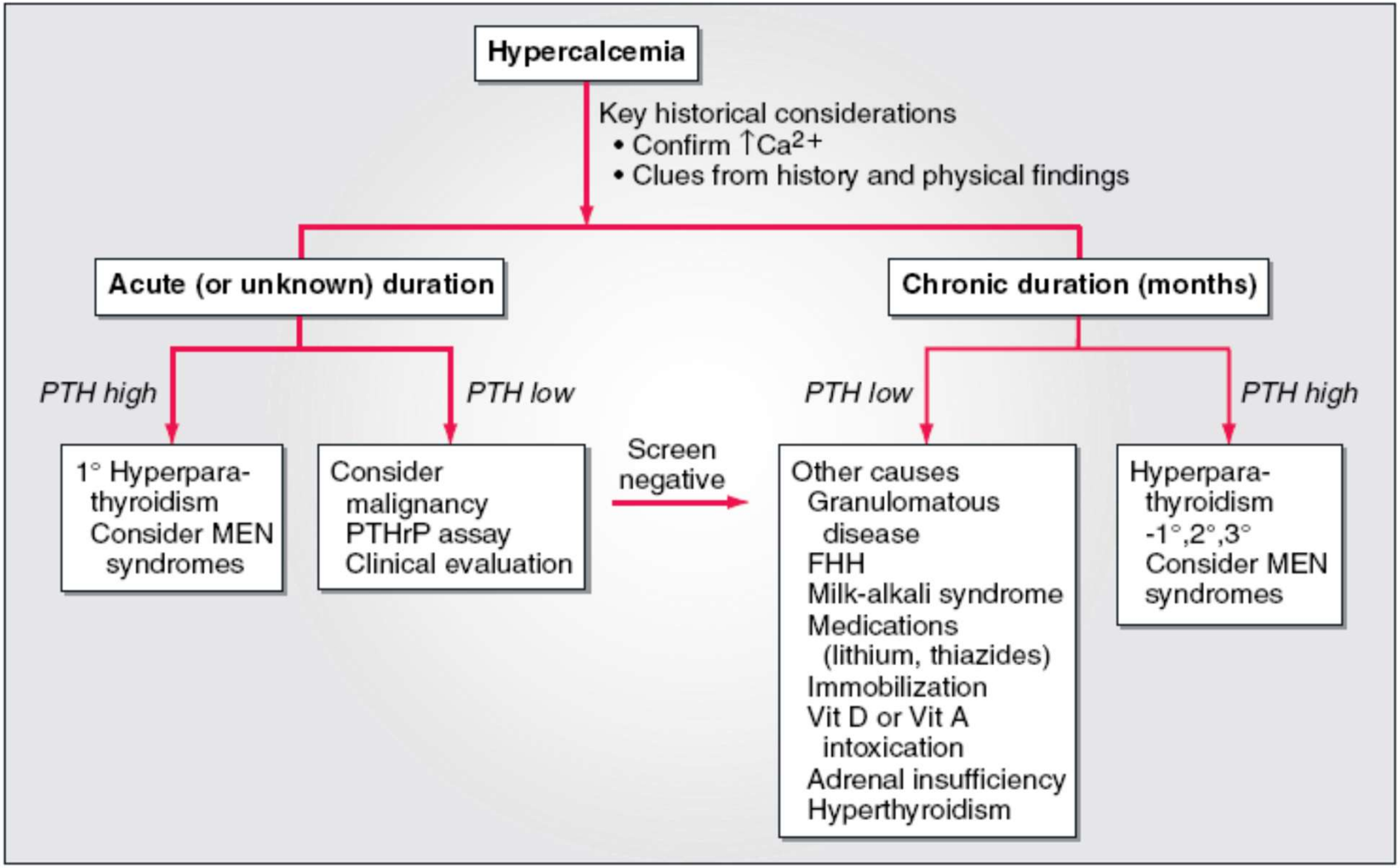


FIGURE 332-5 Algorithm for the evaluation of patients with hypercalcemia. See text for details. FHH, familial hypocalciuric hypercalcemia; MEN, multiple endocrine neoplasia; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related peptide.

Sintomi di IPERCALCEMIA

- Ipertensione arteriosa sistemica
- Ipostenia
- Disturbi gastointestinali lievi
- Ipercalciuria, nefrolitiasi, coliche renali
- Nefrocalcinosi con danno renale, inibizione del riassorbimento tubulare di acqua e sodio con disidratazione
- Riduzione massa ossea
- Stato confusionale (se calcio totale >12mg/dl – 3mmol/l)

- Concentrazioni >16mg/dl (>4mmol/l) sono potenzialmente letali e considerate emergenza medica

Clinical features of hypercalcemia

Symptoms[†]	Signs[†]
None* (~60%)	
Cardiovascular	
	Hypertension (~50%)
Neurological and ophthalmological	
Malaise and fatigue (~30%)	Mental obtundation (~5%)
Depression (~30%)	Dementia (~5%)
Muscle weakness (~10%)	Band keratopathy[+] (~<1%)
	Cognitive impairment (~5%)
	Coma (~<1%)
Gastrointestinal	
Constipation (~30%)	Epigastric tenderness (~5%)
Anorexia (~30%)	
Nausea and vomiting (~10%)	
Renal	
Polydipsia (~30%)	
Polyuria (~30%)	
Renal colic (~10%)	
Rheumatological	
Joint pains (~10%)	Joint swelling (~1%)
Bone pains (~10%)	Bone deformity (~<1%)
	Fractures (~<1%)

[*] Most patients with hypercalcemia are now picked up on routine testing with few symptoms and even fewer signs.
[†] The frequency of symptoms and signs is dependent on the degree of hypercalcemia and its cause, so the percentage frequencies are very approximate.
[+] An ophthalmological sign seen only in very severe cases

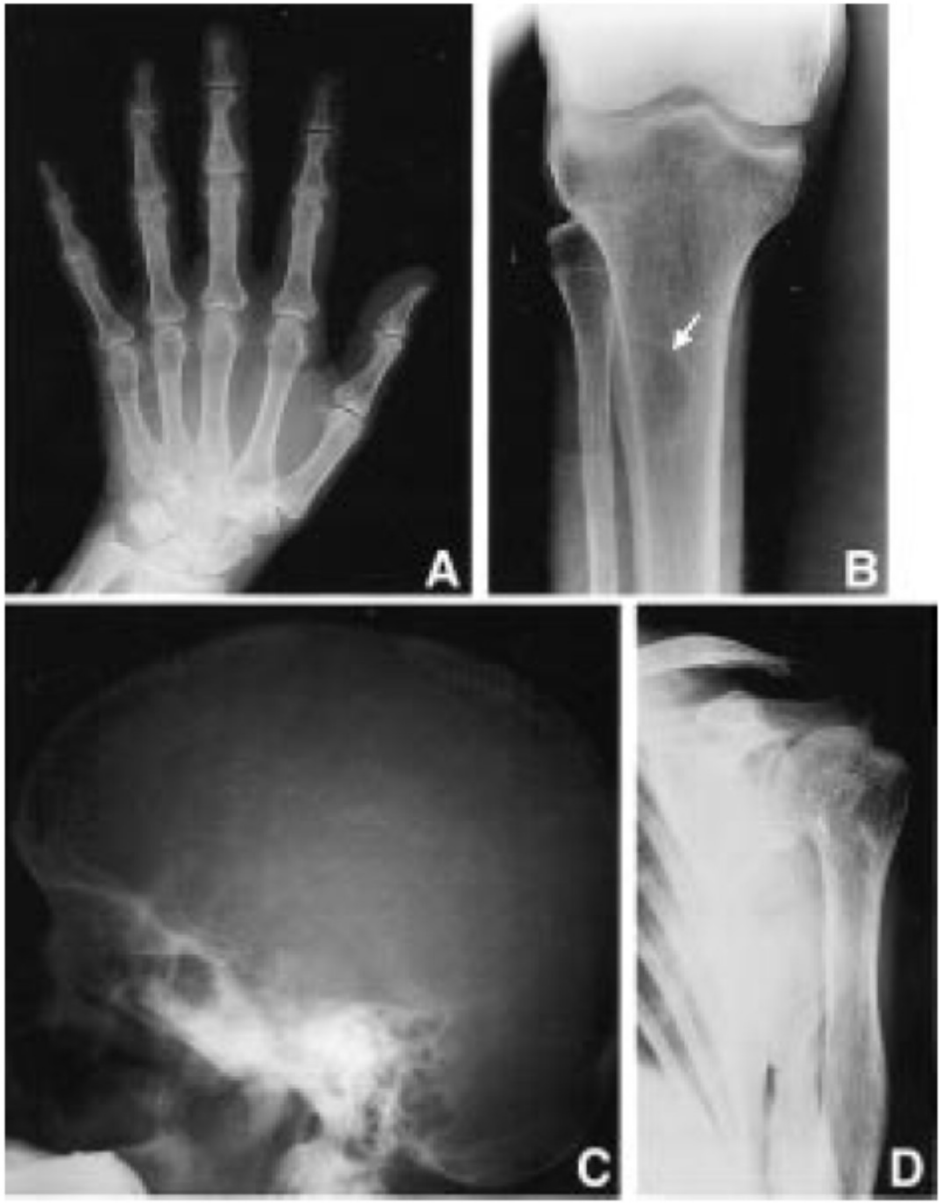


Figure 1: **Radiographic manifestations of PHP**
A=subperiosteal resorption of radial side of middle phalanges and distal tufts; B="brown tumour" (arrow) in the proximal tibia; C=resorption and tapering of distal clavicle; and D=cystic changes in head of humerus.

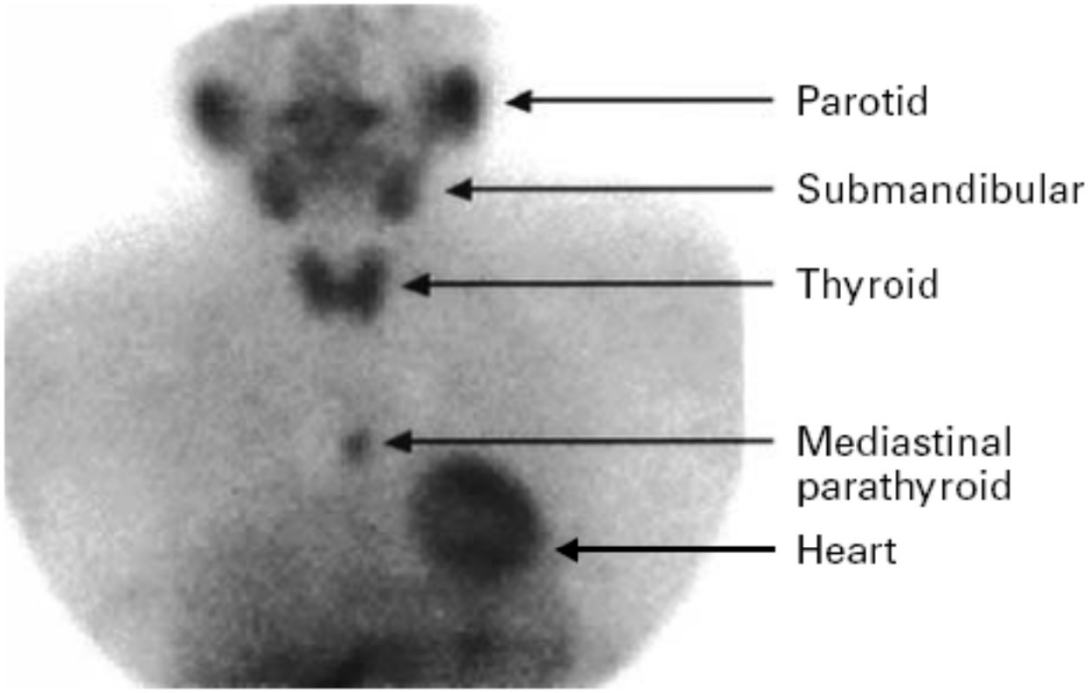


Figure 4. Anterior Planar Image of the Neck and Chest of a Patient with Primary Hyperparathyroidism Obtained with Technetium-99m Sestamibi, Showing a Parathyroid Adenoma in the Mediastinum.

The patient had undergone an unsuccessful parathyroid exploration. The image shown was obtained two hours after the administration of 20 mCi of the radionuclide. The lobes of the thyroid and the salivary glands are clearly visible. (Image courtesy of Dr. Clara Chen.)

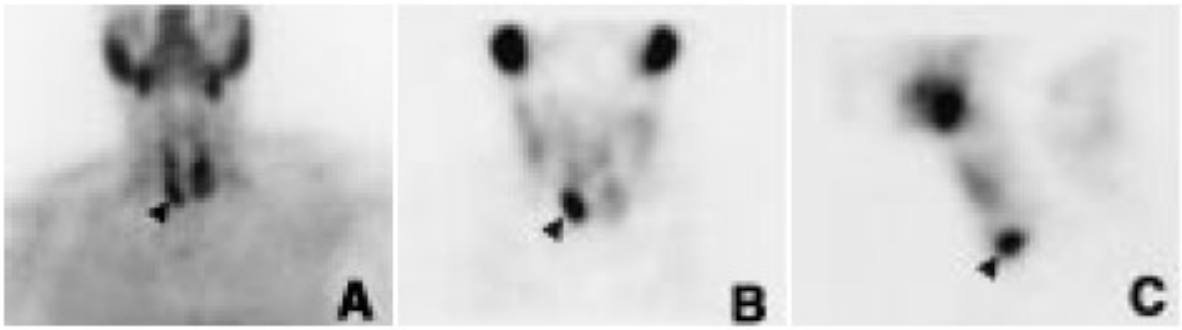


Figure 2: **Technetium-99m sestamibi/iodine scans in planar (A), coronal (B), and sagittal (C) views**

A=increased uptake of the radiotracer in right lower parathyroid adenoma and thyroid in early image (after 20 min); B=after 2 h, concentration of radiotracer in parathyroid adenoma with disappearance of thyroid uptake; C=confirms concentration in parathyroid adenoma.

TABLE 1. CATEGORIES OF PRIMARY HYPERPARATHYROIDISM.*

CHARACTERISTIC	SPORADIC ADENOMA	MULTIPLE ENDOCRINE NEOPLASIA TYPE 1	FAMILIAL HYPOCALCIURIC HYPERCALCEMIA	NEONATAL SEVERE PRIMARY HYPERPARATHYROIDISM
Inheritance	Not inherited	Autosomal dominant	Autosomal dominant	Autosomal recessive
Age at onset of hypercalcemia	55 yr	25 yr	Birth	Birth
Urinary calcium excretion	Normal to high	Normal to high	Low to normal	Low to normal
Serum parathyroid hormone concentration	High	High	Normal	Very high
Parathyroid glands				
No. abnormal	One	Multiple	Multiple	Multiple
Enlargement	20 times normal size	5 times normal size	Minimally enlarged	Very enlarged
Clonality	Monoclonal or oligoclonal	Monoclonal or oligoclonal	Polyclonal	Polyclonal
Effectiveness of parathyroidectomy	95% cured	90% cured, but many recur	Surgery not indicated	Total parathyroidectomy required
Pathophysiology	Stepwise acquired mutations of certain genes, such as *MEN1,* promote the emergence of a neoplastic clone in parathyroid gland	Sequential inactivation of both copies (first copy by inheritance) of the *MEN1* gene leads to the growth of one or more neoplastic clones in parathyroid glands	Monoallelic inherited inactivation of the calcium-sensing receptor gene decreases the sensing of serum calcium by parathyroid cells and by renal tubules	Biallelic inactivation of the calcium-sensing receptor gene impairs calcium sensing in parathyroid cells more than does monoallelic inactivation

*All entries are typical for that disorder. Ranges are broad, with overlap (not shown) among categories.

Therapies for Severe Hypercalcemia

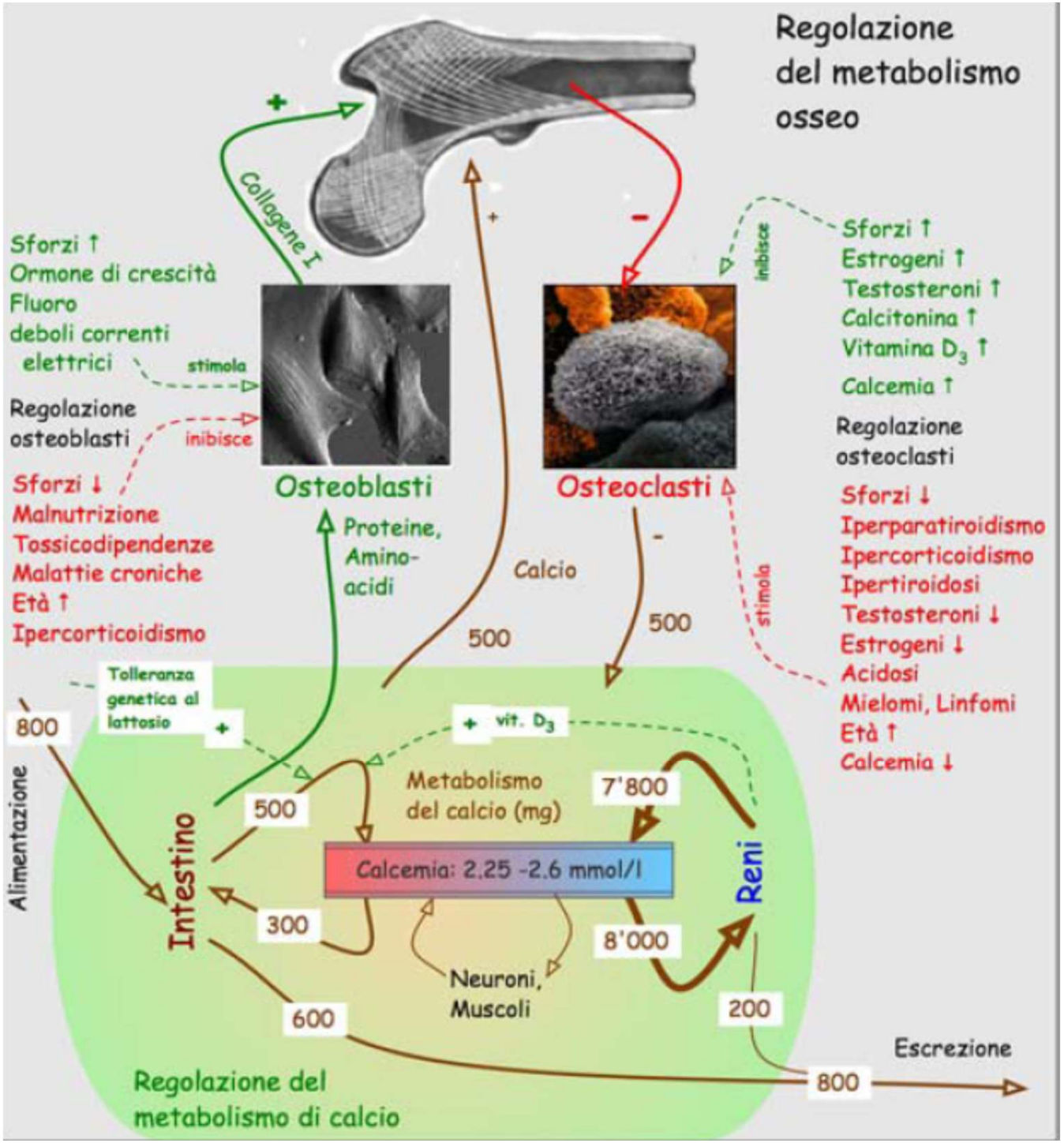
Treatment	Onset of Action	Duration of Action	Advantages	Disadvantages
MOST USEFUL THERAPIES				
Hydration with saline	Hours	During infusion	Rehydration invariably needed	Volume overload, cardiac decompensation, intensive monitoring, electrolyte disturbance, inconvenience
Forced diuresis; saline plus loop diuretic	Hours	During treatment	Rapid action	
Bisphosphonates				
1st generation: etidronate	1–2 days	5–7 days in doses used	First available bisphosphonate; intermediate onset of action	Less effective than other bisphosphonates
2d generation: pamidronate	1–2 days	10–14 days to weeks	High potency; intermediate onset of action	Fever in 20% hypophosphatemia, hypocalcemia, hypomagnesemia
3d generation: zolendronate	1–2 days	>3 weeks	High potency; rapid infusion; prolonged duration of action	Minor; fever, rarely hypocalcemia or hypophosphatemia
Calcitonin	Hours	1–2 days	Rapid onset of action; useful as adjunct in severe hypercalcemia	Rapid tachyphylaxis
Glucocorticoids	Days	Days, weeks	Oral therapy, antitumor agent	Active only in certain malignancies; glucocorticoid side effects
Dialysis	Hours	During use and 24–48 h afterward	Useful in renal failure; onset of effect in hours; can immediately reverse life-threatening hypercalcemia	Complex procedure, reserved for extreme or special circumstances

TABLE 332-5 Functional Classification of Hypocalcemia (Excluding Neonatal Conditions)

PTH ABSENT	
Hereditary hypoparathyroidism	Hypomagnesemia
Acquired hypoparathyroidism	
PTH INEFFECTIVE	
Chronic renal failure	Active vitamin D ineffective
Active vitamin D lacking	Intestinal malabsorption
↓ Dietary intake or sunlight	Vitamin D–dependent rickets type II
Defective metabolism:	Pseudohypoparathyroidism
Anticonvulsant therapy	
Vitamin D–dependent rickets type I	
PTH OVERWHELMED	
Severe, acute hyperphosphatemia	Osteitis fibrosa after parathyroidectomy
Tumor lysis	
Acute renal failure	
Rhabdomyolysis	

Note: PTH, parathyroid hormone.

ipocalcemia


Regolazione del metabolismo osseo
Collagene I
+
-
Sforzi ↑
Ormone di crescità
Fluoro
deboli correnti elettrici
stimola
Regolazione osteoblasti
inibisce
Sforzi ↓
Malnutrizione
Tossicodipendenze
Malattie croniche
Età ↑
Ipercorticoidismo
Osteoblasti
Proteine, Amino-acidi
Calcio
500
500
Osteoclasti
inibisce
Sforzi ↑
Estrogeni ↑
Testosteroni ↑
Calcitonina ↑
Vitamina D_3 ↑
Calcemia ↑
Regolazione osteoclasti
Sforzi ↓
Iperparatiroidismo
Ipercorticoidismo
Ipertiroidosi
Testosteroni ↓
Estrogeni ↓
Acidosi
Mielomi, Linfomi
Età ↑
Calcemia ↓
stimola
Tolleranza genetica al lattosio
+
+ vit. D_3
800
Alimentazione
Intestino
500
Metabolismo del calcio (mg)
7'800
Calcemia: 2.25 -2.6 mmol/l
Reni
300
8'000
Neuroni, Muscoli
600
200
Escrezione
800
Regolazione del metabolismo di calcio

Cause di IPOCALCEMIA

Iperfosfatemia
Insufficienza renale cronica
Rabdomiolisi
Lisi tumorale

Ipoparatiroidismo primitivo
Chirurgico (transitorio o permanente)
Idiopatico(autoimmune)

Pseudoipoparatiroidismo (resistenza all'azione del paratormone)

Deficit o resistenza alla vitamina D (Osteomalacia)

Pancreatite

Metastasi osteoblastiche

Pseudo ipocalcemia
Riduzione dell'albumina sierica

Clinical manifestations of hypocalcemia

disturbances in cellular membrane potential, resulting in neuromuscular irritability.

- **encephalopathy** should be suspected in a patient with unexplained dementia, depression, or psychosis.
- **Muscle cramps, tetany, laryngospasm, or generalized seizures** characteristically results from severe hypocalcemia but can result from reduction in the ionized fraction of plasma Ca without marked hypocalcemia, as occurs in severe alkalosis. Tetany is characterized by sensory symptoms consisting of **paresthesias** of the lips, tongue, fingers, and feet; **carpopedal spasm**, which may be prolonged and painful; generalized muscle aching; and spasm of facial musculature. Tetany may be overt with spontaneous symptoms or latent and requiring provocative tests to elicit. Latent tetany generally occurs at less severely decreased plasma Ca concentrations: 7 to 8 mg/dL (1.75 to 2.20 mmol/L).
- **Chvostek's and Trousseau's signs** are easily elicited at the bedside to identify latent tetany. Chvostek's sign is an involuntary twitching of the facial muscles elicited by a light tapping of the facial nerve just anterior to the exterior auditory meatus. It is present in ≤ 10% of healthy people and in most people with acute hypocalcemia but is often absent in chronic hypocalcemia. Trousseau's sign is the precipitation of carpopedal spasm by reduction of the blood supply to the hand with a tourniquet or BP cuff inflated to 20 mm Hg above systolic BP applied to the forearm for 3 min. Trousseau's sign also occurs in alkalosis, hypomagnesemia, hypokalemia, and hyperkalemia and in about 6% of people with no identifiable electrolyte disturbance.

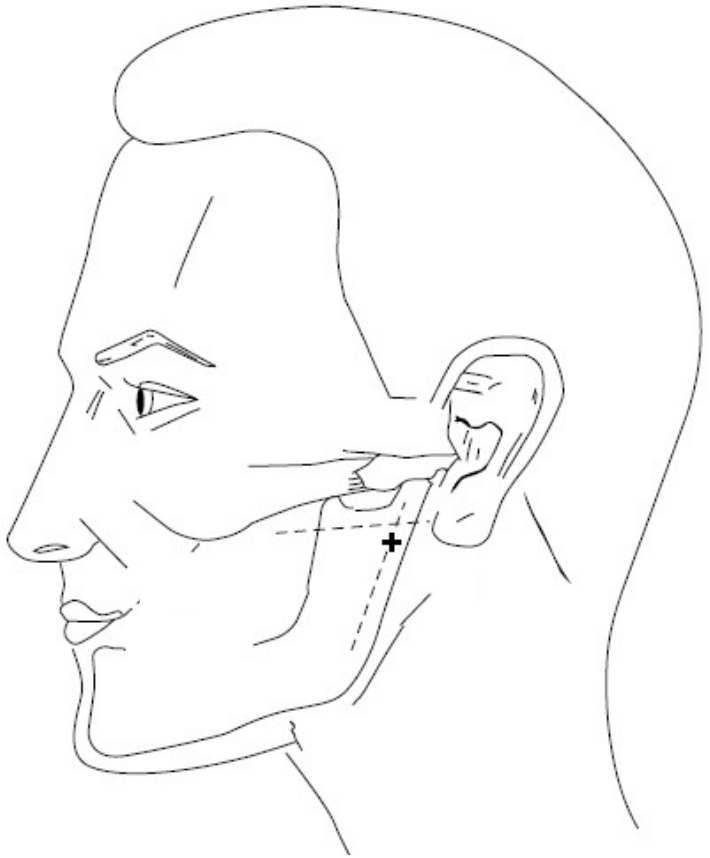
- **Arrhythmia or heart block** occasionally develops in patients with severe hypocalcemia. In hypocalcemia, the ECG typically shows prolongation of the QTc and ST intervals. Changes in repolarization, such as T-wave peaking or inversion, also occur.

- **chronic hypocalcemia,** such as dry and scaly skin, brittle nails, and coarse hair. Candida infections occasionally occur in hypocalcemia but most commonly occur in patients with idiopathic hypoparathyroidism. Cataracts occasionally occur with long-standing hypocalcemia

CHVOSTEK'S SIGN

Elicitation: Tapping on the face at a point just anterior to the ear and just below the zygomatic bone

Postitive response: Twitching of the ipsilateral facial muscles, suggestive of neuromuscular excitability caused by hypocalcemia



TROUSSEAU'S SIGN

Elicitation: Inflating a sphygmomanometer cuff above systolic blood pressure for several minutes

Postitive response: Muscular contraction including flexion of the wrist and metacarpophalangeal joints, hyperextension of the fingers, and flexion of the thumb on the palm, suggestive of neuromuscular excitability caused by hypocalcemia

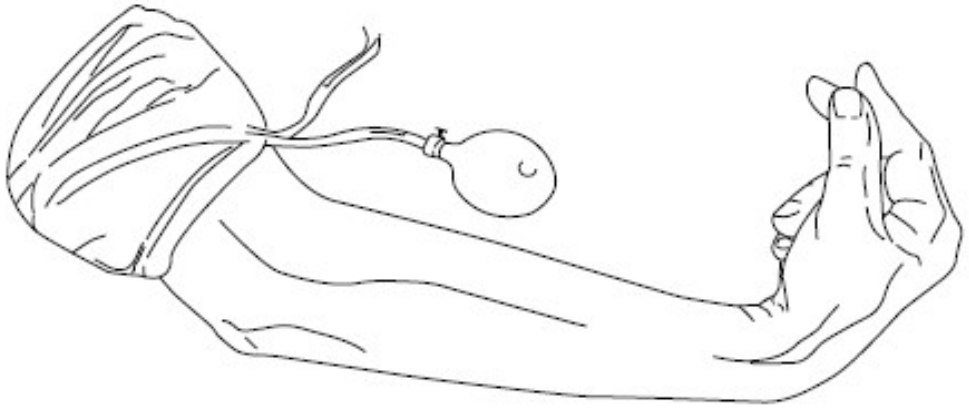


TABLE 2. TREATMENTS FOR HYPERPARATHYROIDISM AND HYPOPARATHYROIDISM.

PROCESS AFFECTED BY TREATMENT	TREATMENTS FOR HYPERPARATHYROIDISM	TREATMENTS FOR HYPOPARATHYROIDISM
Secretion of parathyroid hormone by parathyroid gland	Parathyroidectomy Calcium-sensing–receptor agonist*	Parathyroid autograft
Activation of receptor for parathyroid hormone	Blocker of type 1 receptor*	Parathyroid hormone (1–34)*
Release of calcium from bone	Bisphosphonates Estrogen	
Uptake of calcium from gut	Blocker of vitamin D receptor*	Vitamin D analogue Calcium salts
Excretion of calcium in urine	Forced natriuresis	Thiazide
Exchange with extracorporeal calcium pool	Dialysis	Intravenous calcium

*This treatment is not currently available.

Sintomi di IPOCALCEMIA

- Depressione, demenza, psicosi
- Candidosi cronica
- Tetania

  (solo in presenza di alcalosi o se calcio totale <7mg/dl – 1.75mmol/l o se calcio ionizzato <3mg/dl – 0.75mmol/l)
- Segno di Chovostek
- Segno di Trosseau
- Aritmie

Pathological fracture in a postmenopausal woman

A 75-year-old white woman presents to the **emergency room** with **right wrist pain** after a **fall at home**. She tripped and fell while preparing dinner, and she says that she tried to stop her fall with her outstretched right hand. She heard a “snap” and felt immediate pain. Her medical history is remarkable only for three normal pregnancies, **menopause at age 50 years,** and hypertension that is well controlled with diuretics. She has a 50-pack-year history of **smoking**. Her weight is 45 kg, and her height is 168 cm (**BMI, 16 kg/m^2**). Her examination is remarkable for normal vital signs; a swollen, deformed right distal forearm and wrist, with limited mobility because of pain; and good radial pulses and capillary refill in the right fingernail beds. An x-ray confirms a **fracture of the right radial head**, and the radiologist notes **osteopenia**.

What risk factor for fracture is this woman likely to have?
What are the causes of this condition?
What can her physician offer her to prevent future fractures?

Pathological fracture in a postmenopausal woman

A 75-year-old white woman presents to the **emergency room** with **right wrist pain** after a **fall at home**. She tripped and fell while preparing dinner, and she says that she tried to stop her fall with her outstretched right hand. She heard a "snap" and felt immediate pain. Her medical history is remarkable only for three normal pregnancies, **menopause at age 50 years,** and hypertension that is well controlled with diuretics. She has a 50-pack-year history of **smoking**. Her weight is 45 kg, and her height is 168 cm (**BMI, 16 kg/m^2**). Her examination is remarkable for normal vital signs; a swollen, deformed right distal forearm and wrist, with limited mobility because of pain; and good radial pulses and capillary refill in the right fingernail beds. An x-ray confirms a **fracture of the right radial head**, and the radiologist notes **osteopenia**.

What risk factor for fracture is this woman likely to have? *Osteoporosis*

What are the causes of this condition? *Decreased bone strength as a consequence of demineralization and increased bone turnover as a result of decreased levels of sex steroids (estrogen and testosterone), medications, other hormonal conditions, or diseases of decreased calcium absorption. Additional risk factors: smoking and malnutrition*

What can her physician offer her to prevent future fractures? *Several medications are available to increase bone density (biphosphonates), which may decrease the risk of future fractures. Also, her physician would want to work with her to prevent future falls by limiting unnecessary medications that may cause instability, making changes in the home environment, and evaluating her gait, visual acuity, and peripheral sensory system. The patient should be advised to quit smoking.*

CFIM n° 51

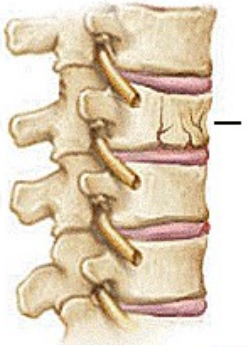
osteoporosis

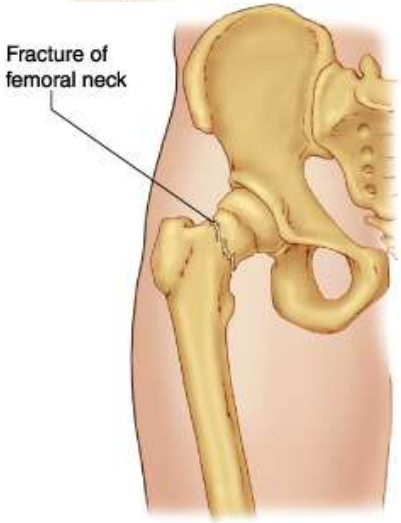
Osteoporosis implies reduced bone mass. It may be 1° (age-related) or 2° to another condition or drugs. If trabecular bone is affected, crush fractures of vertebrae are common (hence the 'littleness' of little old ladies and their dowager's hump); if cortical bone is affected, long bone fractures are more likely, eg femoral neck: the big cause of death and orthopaedic expense (80% hip fractures in the UK occur in women >50yrs).

Prevalence (in those >50yrs): ♂6%, ♀18%. Women lose trabeculae with age, but in men, although there is reduced bone formation, numbers of trabeculae are stable and their lifetime risk of fracture is less.

Risk factors Age-independent risk factors for 1° osteoporosis: parental history, alcohol >4 units daily, rheumatoid arthritis, BMI <22, prolonged immobility, and untreated menopause. See BOX 2 for other risk factors, including for 2° osteoporosis.

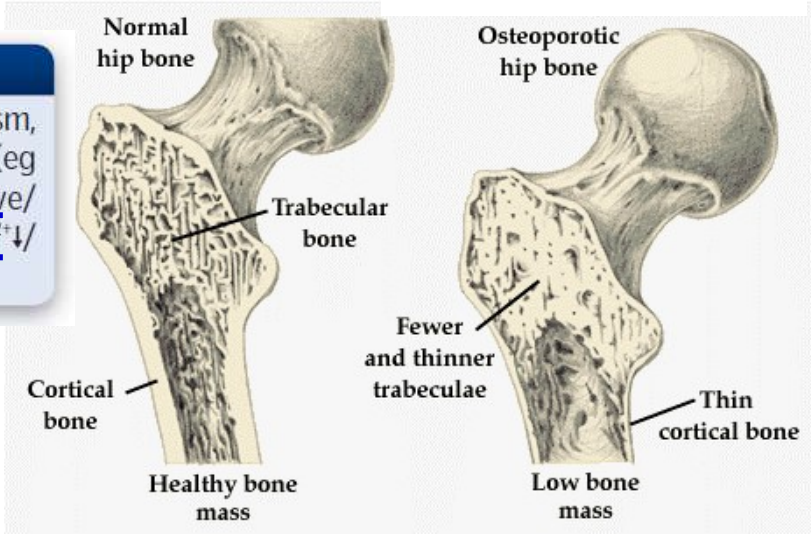
Investigations X-ray (low sensitivity/specificity, often with hindsight after a fracture). Bone densitometry (DEXA—see BOX 1). Bloods: Ca^{2+}, PO_4^{3-} & alk phos normal. Consider specific investigations for 2° causes if suggestive history. Biopsy is unreliable and unnecessary with non-invasive techniques available.





Osteoporosis risk factors 'SHATTERED'

Steroid use of >5mg/d of prednisolone; **H**yperthyroidism, hyperparathyroidism, hypercalciuria; **A**lcohol and tobacco use↑; **T**hin (BMI <22); **T**estosterone↓ (eg antiandrogen ca prostate ℞); **E**arly menopause; **R**enal or liver failure; **E**rosive/inflammatory bone disease (eg myeloma or rheumatoid arthritis); **D**ietary Ca^{2+}↓/malabsorption; diabetes mellitus type 1.



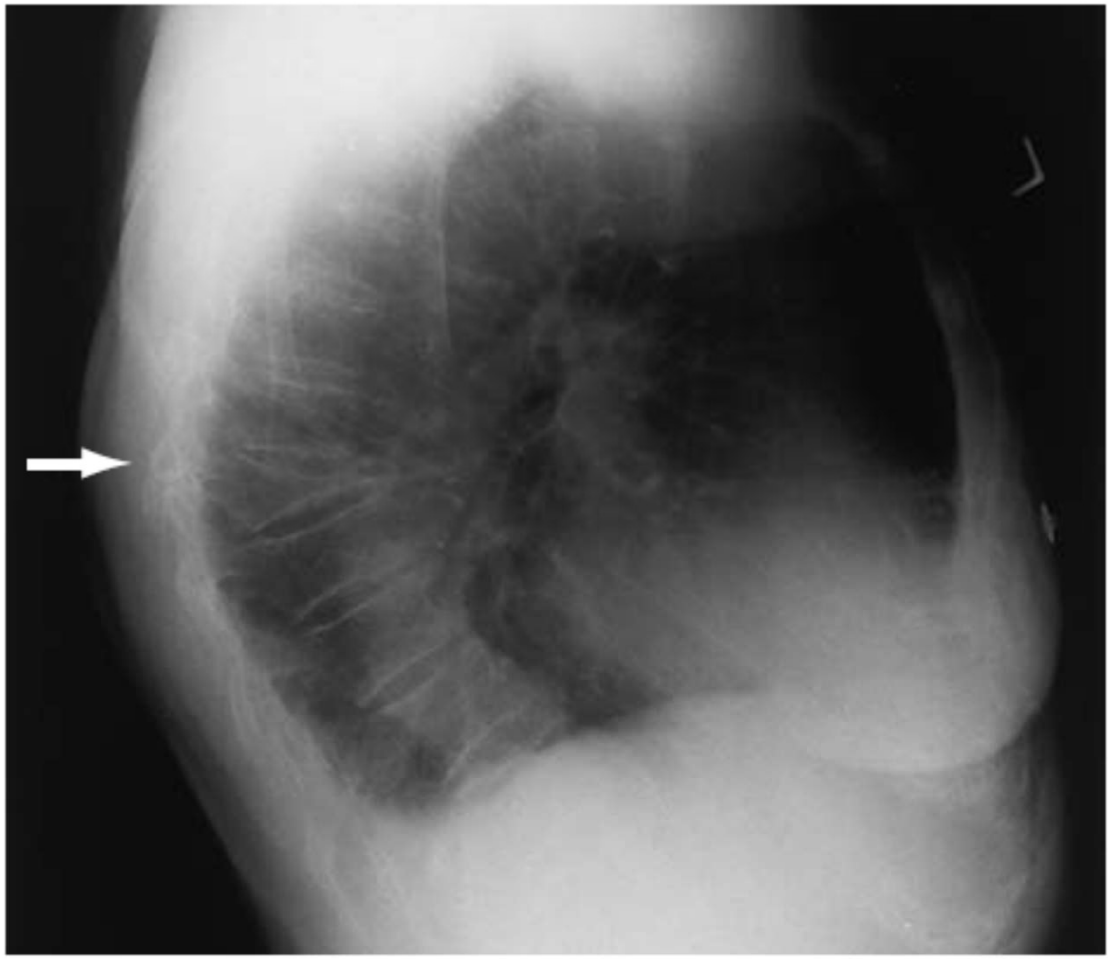
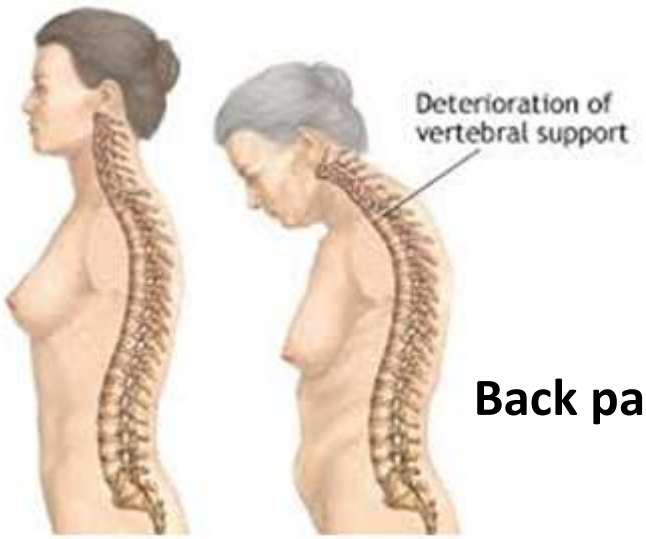
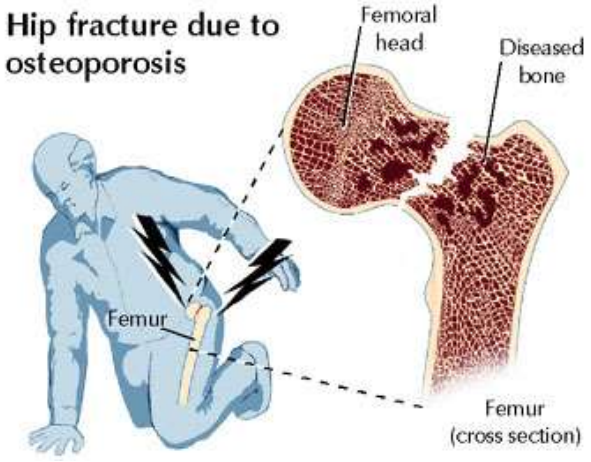


FIGURE 333-2 Lateral spine x-ray showing severe osteopenia and a severe wedge-type deformity (severe anterior compression).



Back pain



Management Loss of bone mineral density may not be entirely irreversible. Age, number of risk factors and bone mineral density (DEXA scan; see BOX) guide the pharmacological approach (eg FRAX, which is a WHO risk assessment tool for estimating 10-yr risk of osteoporotic fracture in untreated patients; see www.shef.ac.uk/frax),[14,15] although DEXA is not necessary if age >75yrs. Lifestyle measures should apply to all (including those at risk but not yet osteoporotic).

Lifestyle measures:

- Quit smoking and reduce alcohol consumption.
- Weight-bearing exercise may increase bone mineral density.[16]
- Balance exercises such as tai chi reduce risk of falls.
- Calcium and vitamin D-rich diet (use supplements if diet is insufficient—see below).
- Home-based fall-prevention programme, with visual assessment and a home visit. NB: hip-protectors are unreliable for preventing fractures.[17]

Pharmacological measures:

- Bisphosphonates: alendronate is 1st line (10mg/d or 70mg/wk; not if eGFR <35). Use also for prevention in long-term steroid use. If intolerant, try etidronate or risedronate. Say to swallow pills with *plenty* of water while remaining upright for >30min and wait 30min before eating or other drugs. (SE: photosensitivity; GI upset; oesophageal ulcers—stop if dysphagia or abdo pain; rarely, jaw osteonecrosis).
- Calcium and vitamin D: rarely used alone for prophylaxis, as questionable efficacy and some evidence of a small increased CV risk. Offer if evidence of deficiency, eg calcium 1g/d + vit D 800U/d. Target serum 25-hydroxy-vitamin D level ≥75nmol/L.
- Strontium ranelate helps ↓ fracture rates, and is an alternative in those intolerant of bisphosphonates. Strontium is in the same periodic group as calcium and reduces reabsorption, and may promote new bone formation.
- Hormone replacement therapy (HRT) can prevent (not treat) osteoporosis in postmenopausal women. Relative risk of breast cancer is 1.4 if used >10yrs; ↑CV risk.
- Raloxifene is a selective oestrogen receptor modulator (SERM) that acts similarly to HRT, but with ↓ breast cancer risk.
- Teriparatide (recombinant PTH) is useful in those who suffer further fractures despite treatment with other agents. There is a potential ↑ risk of renal malignancy.
- Calcitonin may reduce pain after a vertebral fracture.
- Testosterone may help in hypogonadal men by promoting trabecular connectivity.
- Denosumab, a monoclonal Ab to RANK ligand, given SC twice yearly ↓ reabsorption.

Vitamin D sufficiency is estimated by measuring 25-hydroxyvitamin D (25[OH]D or calcidiol) concentrations. The range of common agreement is 30 to 40 ng/mL (75 to 100 nmol/L). Experts agree that levels lower than 20 ng/mL are suboptimal for skeletal health.

We suggest supplementation with cholecalciferol rather than ergocalciferol when available.

●Vitamin D3 (cholecalciferol) is available in 400, 800, 1000, 2000, 5000, 10,000, and 50,000 unit capsules. It is available in some countries as an intramuscular injection, which can be extremely painful.

●Vitamin D2 (ergocalciferol) is available for oral use in 400 and 50,000 unit capsules or in a liquid form (8000 unit/mL [200 mcg/mL]).

2. Bisphosphonates—Bisphosphonate therapy is indicated for patients with a pathologic spine fracture or a low-impact hip fracture, and for patients with osteoporosis, defined as a DXA T score of –2.5 or less in the spine, total hip, or femoral neck. Bisphosphonates all work similarly, inhibiting osteoclast-induced bone resorption. They

3. Denosumab—Denosumab (Prolia, Xgeva) is a monoclonal antibody that inhibits the proliferation and maturation of preosteoclasts into mature osteoclast bone-resorbing cells. It does this by binding to the osteoclast receptor activator of nuclear factor-kappa B ligand (RANKL).

4. Teriparatide—Teriparatide (Forteo, Parathar) is an analog of PTH. Teriparatide stimulates the production of new collagenous bone matrix that must be mineralized. Patients

DEXA bone densitometry: WHO osteoporosis criteria

Dual Energy X-ray Absorptiometry

It is better to scan the hip than the lumbar spine. Bone mineral density (g/cm^2) is compared with that of a young healthy adult. The 'T-score' is the number of standard deviations (SD, p765) the bone mineral density (BMD) is from the youthful average. Each decrease of 1 SD in bone mineral density ≈ 2.6-fold ↑ in risk of hip fracture.

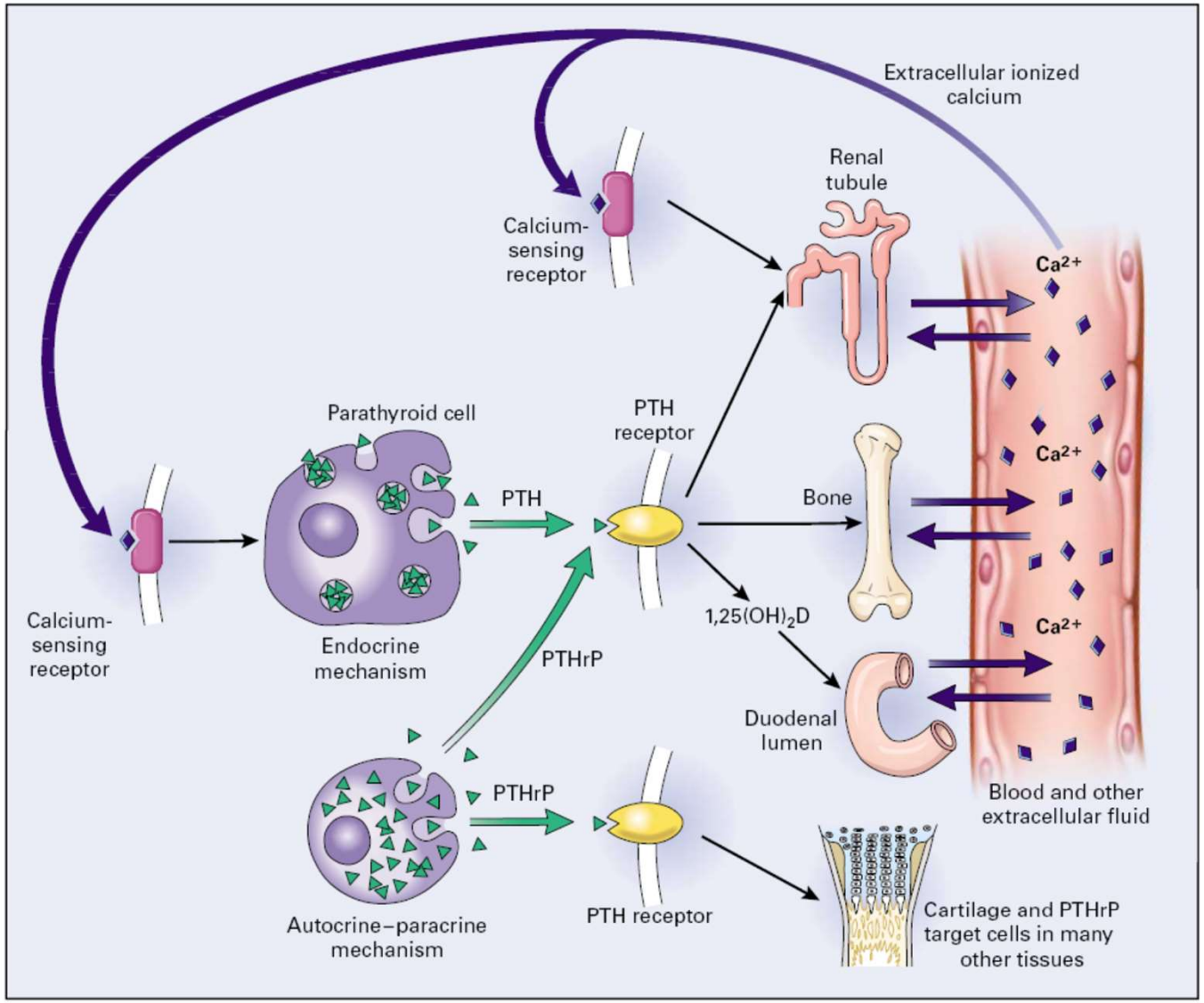
T-score > 0	BMD is better than the reference.
0 to -1	BMD is in the top 84%: no evidence of osteoporosis.
-1 to -2.5	Osteopenia. Risk of later osteoporotic fracture. Offer lifestyle advice.
-2.5 or worse	Osteoporosis. Offer lifestyle advice and treatment (p696). Repeat DEXA in 2yrs.

BMD screening by dual-energy x-ray absorptiometry

- **In all women 65 years of age and older (Grade 2B).**
- **In postmenopausal women less than 65 years if one or more risk factors are present (Grade 2B).**
- Do not perform routine BMD measurements in premenopausal women (Grade 2C)
- Do not perform routine BMD measurements in all men (Grade 2C), but do measure BMD in men who have clinical manifestations of low bone mass, such as radiographic osteopenia, history of low trauma fractures, and loss of more than 1.5 inches in height, as well as in those with risk factors for fracture, such as long-term glucocorticoid therapy, androgen deprivation therapy for prostate cancer, hypogonadism, primary hyperparathyroidism, hyperthyroidism, and intestinal disorders.

Clinical risk factors for fracture

- **Advancing age**
- **Previous fracture**
- **Glucocorticoid therapy**
- **Parental history of hip fracture**
- **Low body weight**
- **Current cigarette smoking**
- **Excessive alcohol consumption**
- **Rheumatoid arthritis**
- **Secondary osteoporosis (eg, hypogonadism or premature menopause, malabsorption, chronic liver disease, inflammatory bowel disease)**



. The Parathyroid Axis.

The synthesis of parathyroid hormone (PTH) and parathyroid hormone–related peptide (PTHrP) is shown on the left, and their target sites of action are shown on the right. Both act by means of the same receptor (also termed the type 1 PTH receptor). Negative feedback of 1,25-dihydroxyvitamin D is not shown. See the text for further descriptions. An excess or deficiency of parathyroid hormone may be treated either at the level of parathyroid hormone release (and the parathyroid hormone receptors) or at selected sites distal to the parathyroid hormone receptors. Blue arrows indicate extracellular calcium flow.

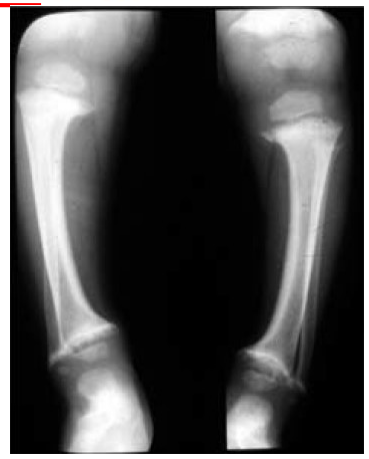
osteomalacia

In osteomalacia there is a normal amount of bone but its mineral content is low (there is excess uncalcified osteoid and cartilage). This is the reverse of osteoporosis in which mineralization is unchanged, but there is overall bone loss. Rickets is the result if this process occurs during the period of bone growth; osteomalacia is the result if it occurs after fusion of the epiphyses.

Causes

- *Vitamin D deficiency:* Due to malabsorption (p280), poor diet, or lack of sunlight.
- *Renal osteodystrophy:* Renal failure leads to 1,25-dihydroxy-cholecalciferol deficiency [$1,25(OH)_2$-vitamin D deficiency]. See also *renal bone disease* (p302).
- *Liver disease:* Due to reduced hydroxylation of vitamin D to 25-hydroxy-cholecalciferol and malabsorption of vitamin D, eg in cirrhosis (p260).

X-ray: In osteomalacia there is a loss of cortical bone;



Typical ragged metaphyseal surfaces are seen in the knee and ankle joints of a child with rickets, with bowing of the long bones (fig 2) Rickets.

Treatment

- In dietary insufficiency, give vitamin D, eg as one Calcium D_3 Forte tablet/12h PO.
- In malabsorption or hepatic disease, give vitamin D_2 (ergocalciferol), up to 40,000U (=1mg) daily, or parenteral calcitriol, eg 7.5mg monthly.
- If due to renal disease or vitamin D resistance, give alfacalcidol (1α-hydroxy-vitamin D_3) 250ng–1µg daily, or calcitriol (1,25-dihydroxy-vitamin D_3) 250ng–1µg daily, and adjust dose according to plasma Ca^{2+}. ▶▶Alfacalcidol and calcitriol can cause dangerous hypercalcaemia.
- Monitor plasma Ca^{2+}, initially weekly, and if nausea/vomiting.

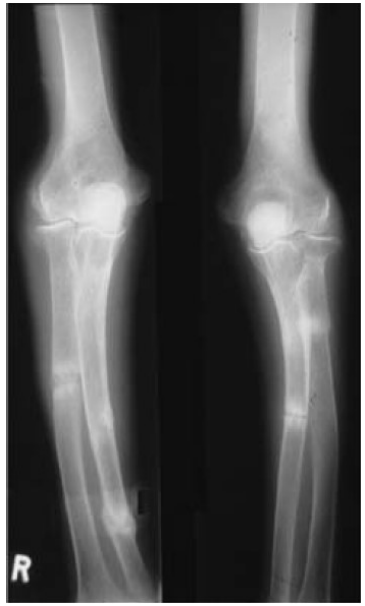
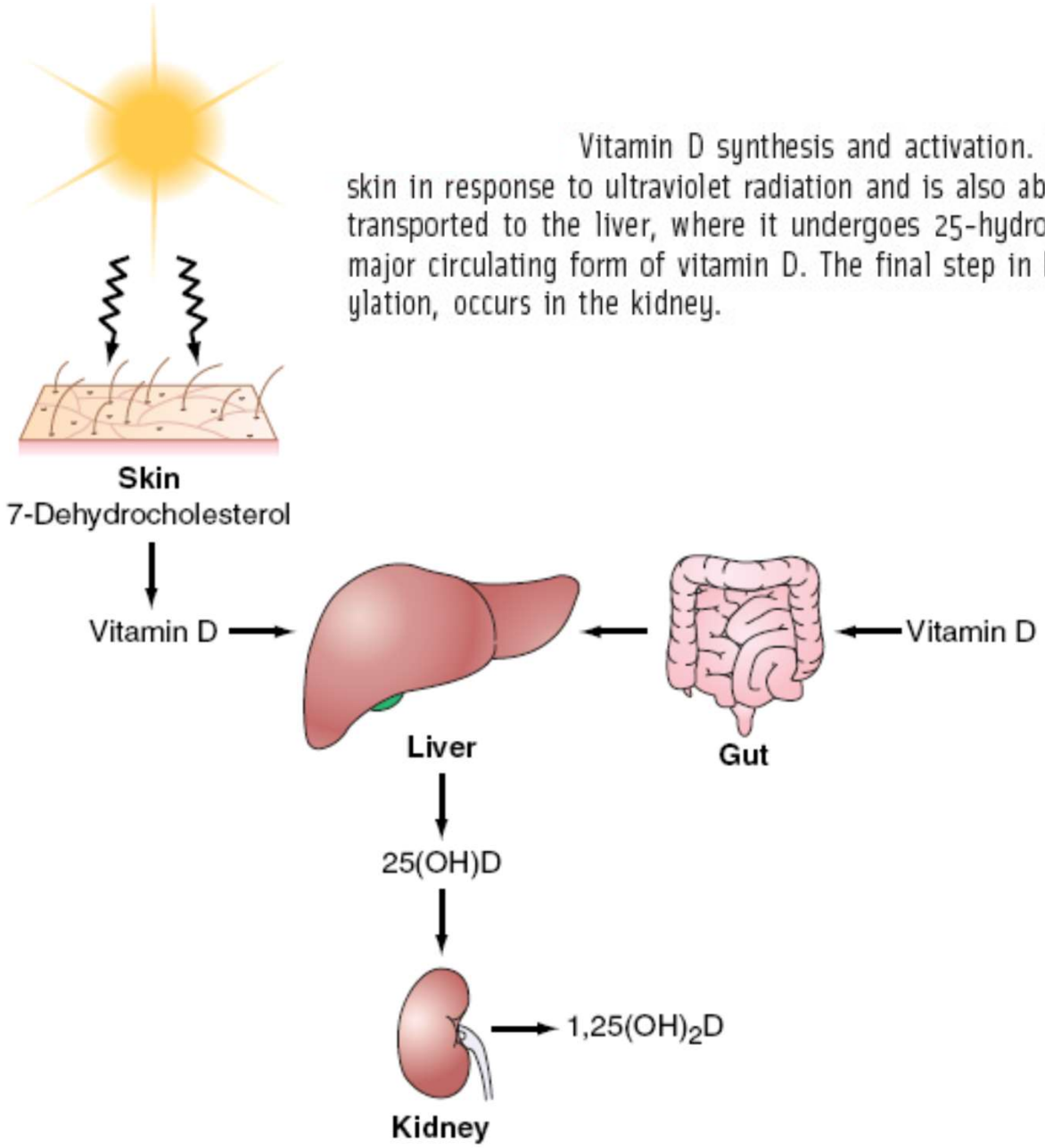


Fig 1. Osteomalacia.
Cortical bone lucency and Looser's zones are seen in both forearms of a patient with osteomalacia



Vitamin D synthesis and activation. Vitamin D is synthesized in the skin in response to ultraviolet radiation and is also absorbed from the diet. It is then transported to the liver, where it undergoes 25-hydroxylation. This metabolite is the major circulating form of vitamin D. The final step in hormone activation, 1α-hydroxylation, occurs in the kidney.

Which of the following patients is most likely to be a candidate for bone mineral density screening?

A. A 65-year-old, thin, white woman who smokes and is 15 years postmenopausal
B. A 40-year-old white woman who exercises daily and still menstruates
C. A healthy 75-year-old white man who is sedentary
D. A 60-year-old overweight African American woman
E. A 35-year-old asthmatic woman who took prednisone 40 mg/d for a 2-week course 1 week ago

Which of the following patients is most likely to be a candidate for bone mineral density screening?

A. A 65-year-old, thin, white woman who smokes and is 15 years postmenopausal
B. A 40-year-old white woman who exercises daily and still menstruates
C. A healthy 75-year-old white man who is sedentary
D. A 60-year-old overweight African American woman
E. A 35-year-old asthmatic woman who took prednisone 40 mg/d for a 2-week course 1 week ago

A. Of the choices, this woman is the only individual with risk factors. Risk factors include white race, age, postmenopausal status, smoking, positive family history, poor nutritional status, and chronic treatment with a drug known to predispose to bone loss.

Metabolic bone diseases: Paget's disease of bone

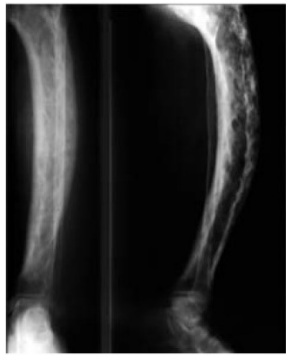
Also called *osteitis deformans*, there is increased bone turnover associated with increased numbers of osteoblasts and osteoclasts with resultant remodelling, bone enlargement, deformity, and weakness. Rare in the under-40s. Incidence rises with age (3% over 55yrs old). Commoner in temperate climates, and in Anglo-Saxons.

Clinical features Asymptomatic in ~70%. Deep, boring pain, and bony deformity and enlargement—typically of the pelvis, lumbar spine, skull, femur, and tibia (classically a bowed sabre tibia; fig 3). *Complications* include pathological fractures, osteoarthritis, ↑Ca^{2+}, nerve compression due to bone overgrowth (eg deafness, root compression), high-output CCF (if >40% of skeleton involved) and osteosarcoma (<1% of those affected for >10yrs—suspect if sudden onset or worsening of bone pain).[20]

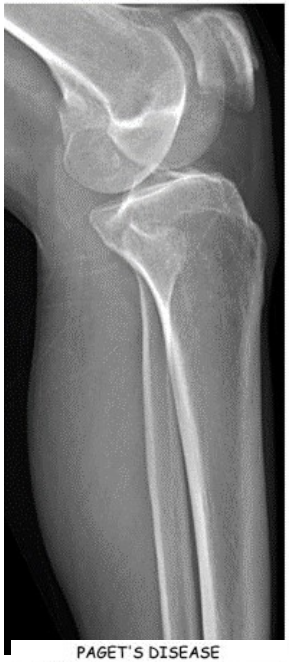
Radiology X-ray Localized enlargement of bone. Patchy cortical thickening with sclerosis, osteolysis, and deformity (eg *osteoporosis circumscripta* of the skull). Affinity for axial skeleton, long bones, and skull. Bone scan may reveal 'hot spots'.

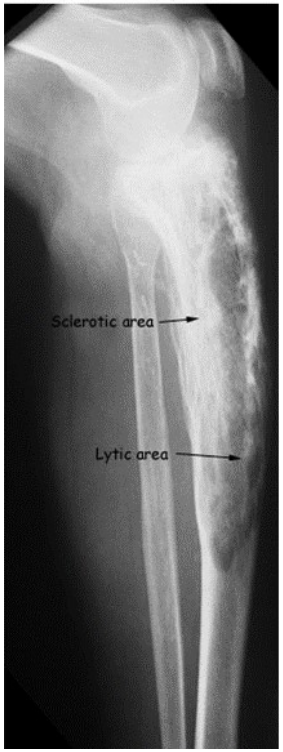
Blood chemistry Ca^{2+} and PO_4^{3-} normal; alk phos markedly raised.

Treatment If analgesia fails, alendronate may be tried to reduce pain and/or deformity. It is more effective than etidronate or calcitonin, and as effective as IV pamidronate. Follow expert advice.



The 'sabre tibia' seen in Paget's disease, with multiple sclerotic lesions





Clinical manifestations and diagnosis of Paget disease of bone (UpToDate)

● Paget disease of bone (PDB) is a fairly common finding in aging bone; it is often asymptomatic. **Its onset is typically after age 55**, with a slight predominance in men. It is common in England, Scotland, Central Europe, and Greece, as well as in countries and cities settled by European immigrants. Within these countries, there are geographical clusters of disease. **Estimates of prevalence in some populations range from 3 percent in patients over 40 to up to 9 percent in older adults.**

● PDB is characterized by abnormalities of the **osteoclast**; there are accelerated bone turnover and abnormal bone remodeling. Both genetic and environmental causes are thought to contribute to its pathogenesis.

● The majority of patients with PDB are **asymptomatic**. Symptoms are usually due to overgrowth of the affected bone. **Pain** may arise **directly, from a pagetic lesion in bone**, or from secondary causes, including **osteoarthritis**, fracture, **nerve impingement**, or, rarely, tumor. Paget disease has a predilection for the **skull**, **thoracolumbar spine**, **pelvis**, **long bones of the lower extremities**. The common clinical manifestations include bone pain or chronic back pain, bone **deformities**, and **arthritis**, and depend upon the region involved.

● **Osteosarcoma** is a rare, usually fatal complication of PDB.

● Laboratory findings, which reflect increased bone turnover and are typical of untreated disease, include elevated levels of serum **alkaline phosphatase** (sAP) and bone-specific alkaline phosphatase (bAP). The degree of elevation generally reflects the extent and activity of the disease. Serum calcium and phosphorus are normal in most patients.

● **Plain radiographs** reflect the abnormal bone turnover characteristic of disease. A predominantly osteolytic lesion may be seen early in disease. Over time, however, there is evidence of an osteoblast response, and **the bone thickens and enlarges**, with thickened cortices marked by tunneling and accentuated trabeculae at one or more affected skeletal sites. In late disease, there may be dense bone by plain film, with little evidence of remodeling by biochemical parameters.

● **Bone scintigraphy** is more sensitive than plain radiography, particularly in early disease. Increased uptake is seen focally at the sites of active pagetic bone lesions on radionuclide bone scanning.

● **Diagnosis of PDB** in patients with clinical or laboratory findings suggestive of disease is confirmed by the demonstration of characteristic **radiographic changes**. In most patients, the **sAP** is elevated, and additional tests of bone turnover are not required. We obtain a baseline **radionuclide bone scan** to document the extent and locations of skeletal involvement; we perform radiographs of affected sites to identify impending fractures, potential malignant lesions, osteoarthritis, or other bone abnormalities.

● PDB occurs in an **aging population** that also has an increased prevalence of malignancy, osteoarthritis, and osteoporosis.

Bisphosphonates listed in order of increasing potency

Simple bisphosphonates
Etidronate
Tiludronate
Clodronate
Nitrogen-containing bisphosphonates
Pamidronate
Alendronate
Neridronate
Ibandronate
Risedronate
Zoledronic acid

Treatment of Paget disease of bone (UpToDate)

●The goals of pharmacologic treatment for Paget disease are to ease pain and to normalize the rate of bone remodeling. Success of treatment is generally assessed by periodic monitoring of the alkaline phosphatase.

●Symptoms and findings that may respond to pharmacologic treatment in patients with active disease include bone pain, symptoms of nerve compression, and radiographic findings of osteolytic bone lesions.

●Although unproven, treatment with nitrogen-containing bisphosphonates is generally expected to prevent the long-term complications of disease, such as pathologic fractures, skeletal deformity, secondary osteoarthritis, and neurologic disorders including deafness.

●When treatment for Paget disease is indicated, we recommend **a nitrogen-containing bisphosphonate as first-line therapy (Grade 1A).**

●In symptomatic patients, we recommend treatment if the alkaline phosphatase level is elevated (Grade 1A). We also suggest treatment in symptomatic patients if the alkaline phosphatase level is normal but there is evidence of active disease on bone scintigraphy (Grade 2B).

●In asymptomatic patients with active disease (as determined by bone scintigraphy or an increased alkaline phosphatase):

•We suggest treatment if disease is present at sites where complications could occur (eg, skull, spine, weightbearing bones, abutting joint lines) (Grade 2B).

•We suggest treatment if bone surgery is planned on sites with active disease or if the alkaline phosphatase is greater than twice the upper limit of normal (Grade 2C).

●Potential side effects of bisphosphonates include an acute phase response lasting several days, which occurs most commonly but not exclusively with the intravenous medications on initial administration and which can be treated with acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs).

●**In older patients or in those with more extensive disease, we suggest treatment with zoledronic acid (zoledronate) rather than an oral bisphosphonate (Grade 2B).**

●In younger patients or in those with less extensive disease, the choice of nitrogen-containing bisphosphonate can be based upon patient preference for intravenous or oral therapy, availability, and cost.

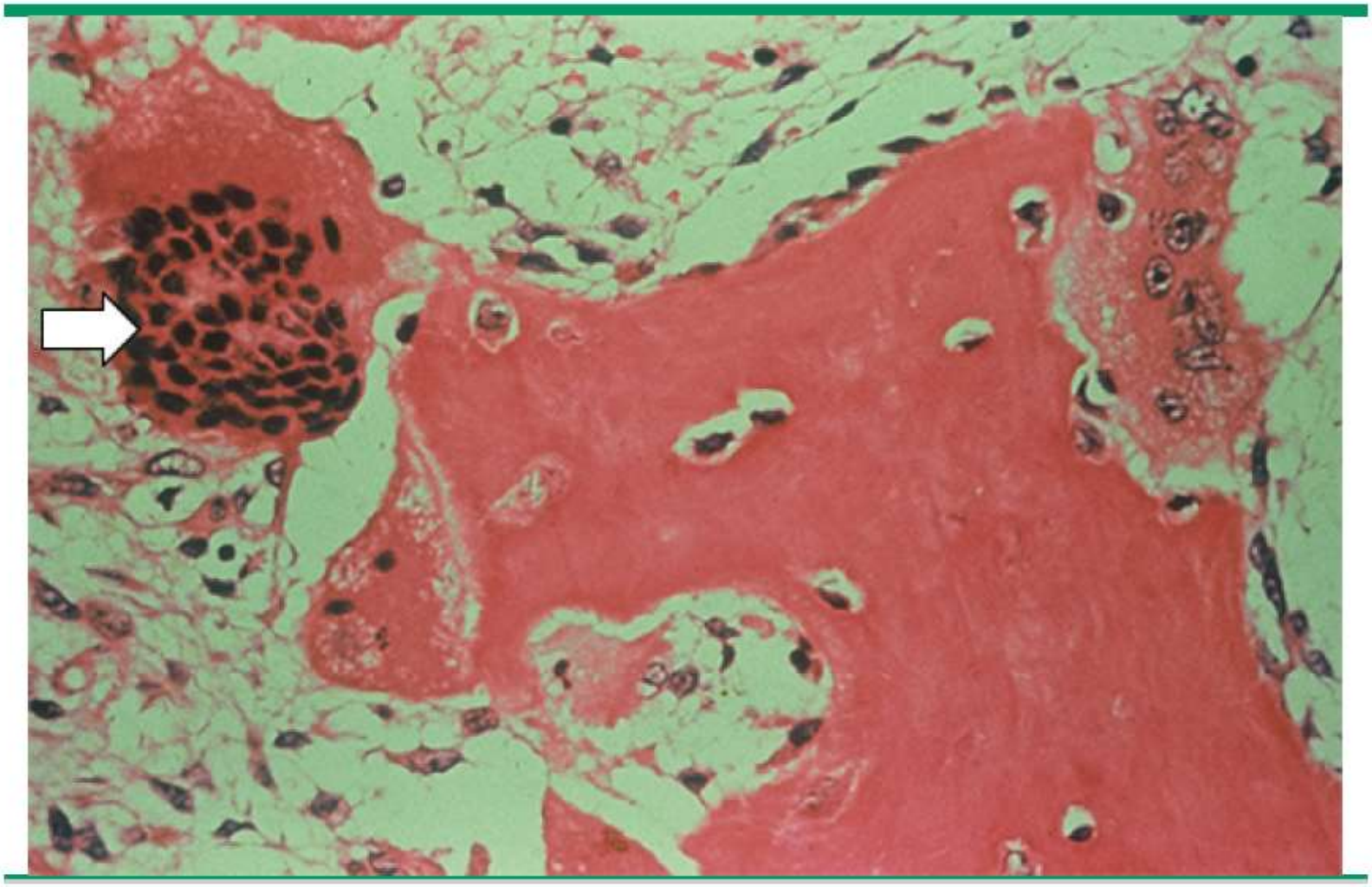
●In the rare patient intolerant of both parenteral and oral bisphosphonates, we suggest treatment with calcitonin (Grade 2C).

●In all patients who will be treated with bisphosphonates, normal serum levels of calcium and 25-hydroxyvitamin D (calcidiol) should be documented, and supplemental vitamin D (800 international units daily) and calcium supplements (1200 mg/day of elemental calcium) should be given to avoid hypocalcemia.

●Because of a small but undetermined level of risk for osteonecrosis of the jaw (ONJ) in association with bisphosphonate use in Paget disease, planned invasive dental work, such as extractions or implants, should be performed at least three to six months prior to institution of bisphosphonate therapy whenever possible. (See 'Side effects of bisphosphonates' above.)

●Indications for retreatment with bisphosphonates generally depend upon evidence of increased or recurrent abnormal bone turnover as determined by periodic serial measurements of serum alkaline phosphatase, radiographic progression of disease, or recurrent pain. New symptoms, which may respond to retreatment if due to Paget disease, should be distinguished from secondary or unrelated changes that are not caused by current disease activity.

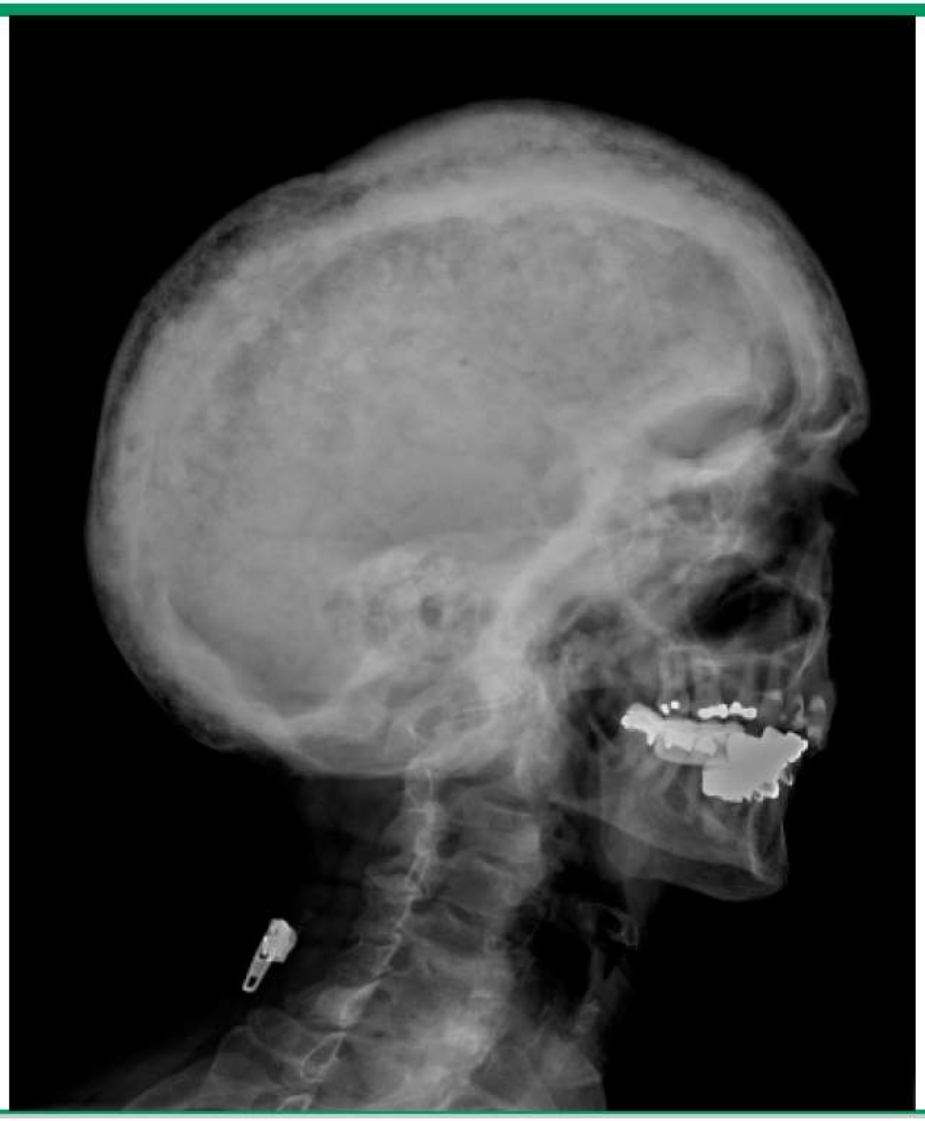
Abnormally large osteoclasts in pagetic bone



Abnormally large, bizarre osteoclasts characterize pagetic bone. There is thickened trabeculae on this H&E stain, with the bone rimmed with osteoblasts and the marrow replaced by stromal cells. Pagetic bone is extremely vascular.

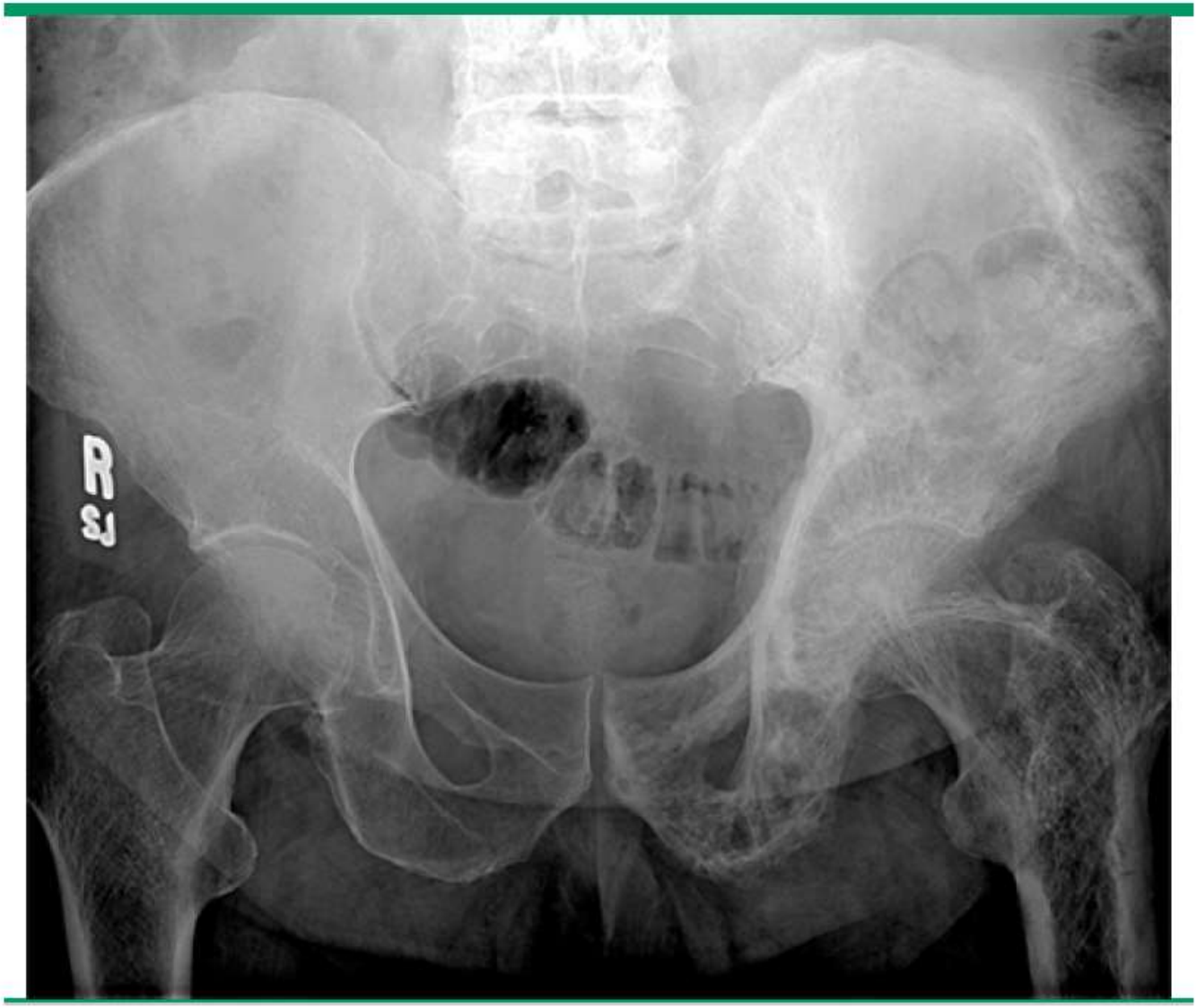
H&E: hematoxylin and eosin.

Lateral skull of an elderly woman with Paget disease



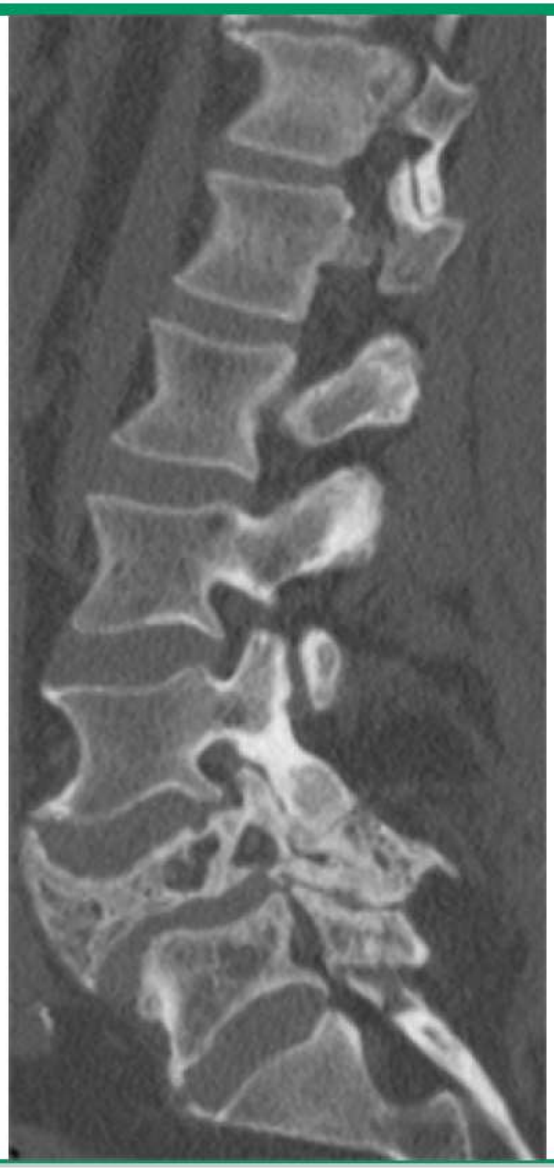
Lateral skull of an older adult woman with Paget disease. Note the thickened table of the skull, the areas of lytic mixed with sclerotic bone, and the appearance of "cotton wool spots" or circular densities of sclerotic bone so characteristic of Paget disease.

Paget disease of the L hemipelvis and L proximal femur



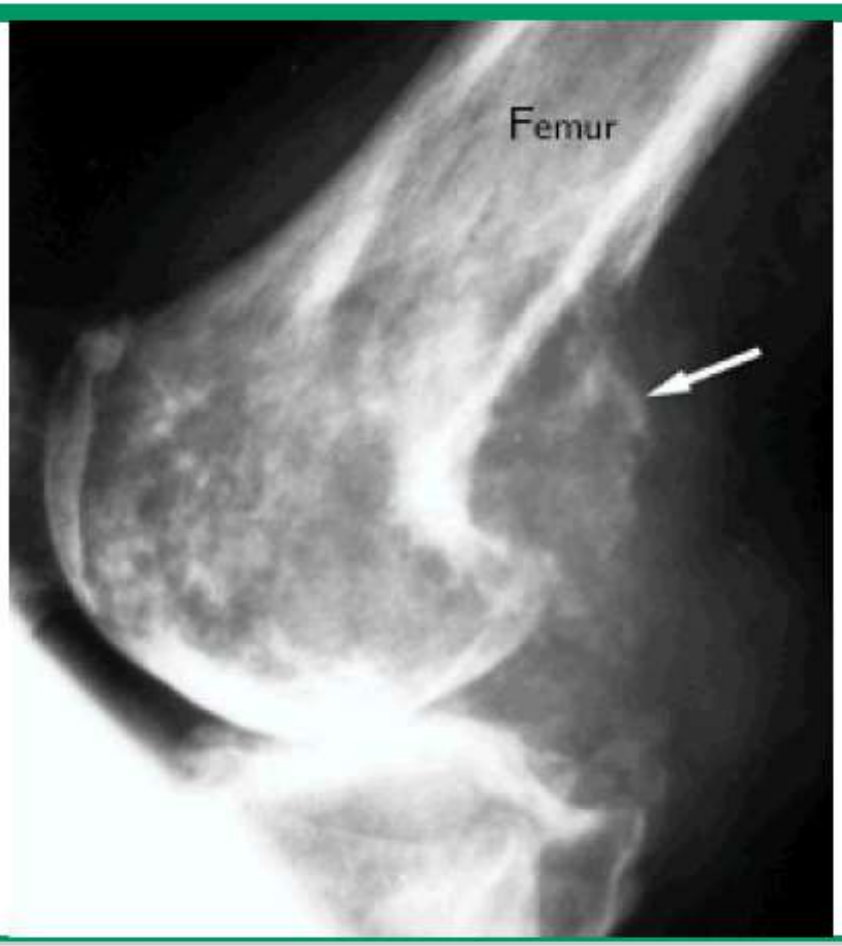
Paget disease of the L hemipelvis and L proximal femur (sparing the R) with coarse remodeling of bone, enlargement, and deformity of the pelvis. There is thickening of the iliopectineal line so characteristic of PDB, with accentuated trabeculae and thickened cortices. Protrusio and loss of joint space are present on the left.

Severe spinal stenosis in Paget disease



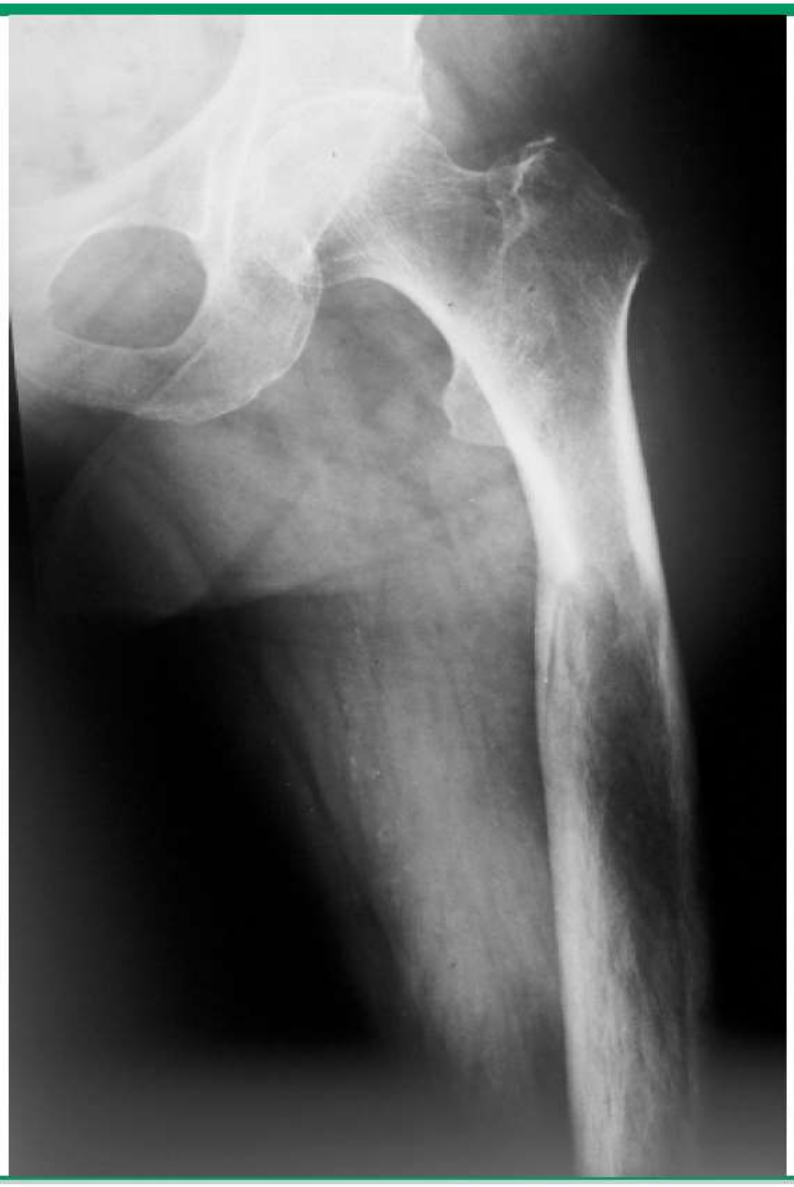
Paget disease affecting L4 and L5, with overgrowth of L4, extension of pagetic changes into the posterior elements of the spine, and compression. This man presented with severe spinal stenosis.

Paget osteosarcoma



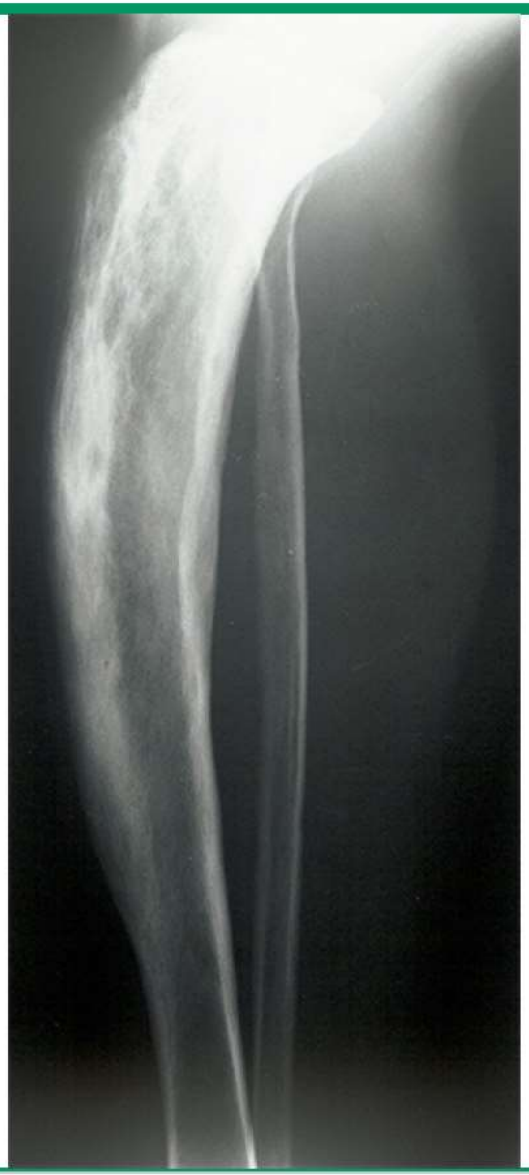
Lateral radiograph in a patient with known Paget disease shows osteosarcoma arising in a pagetic area of the distal right femur. There is soft tissue swelling and destruction of the distal femoral cortex (arrow). Marked trabecular thickening consistent with Paget disease is also seen.

Left femur with Paget disease of bone



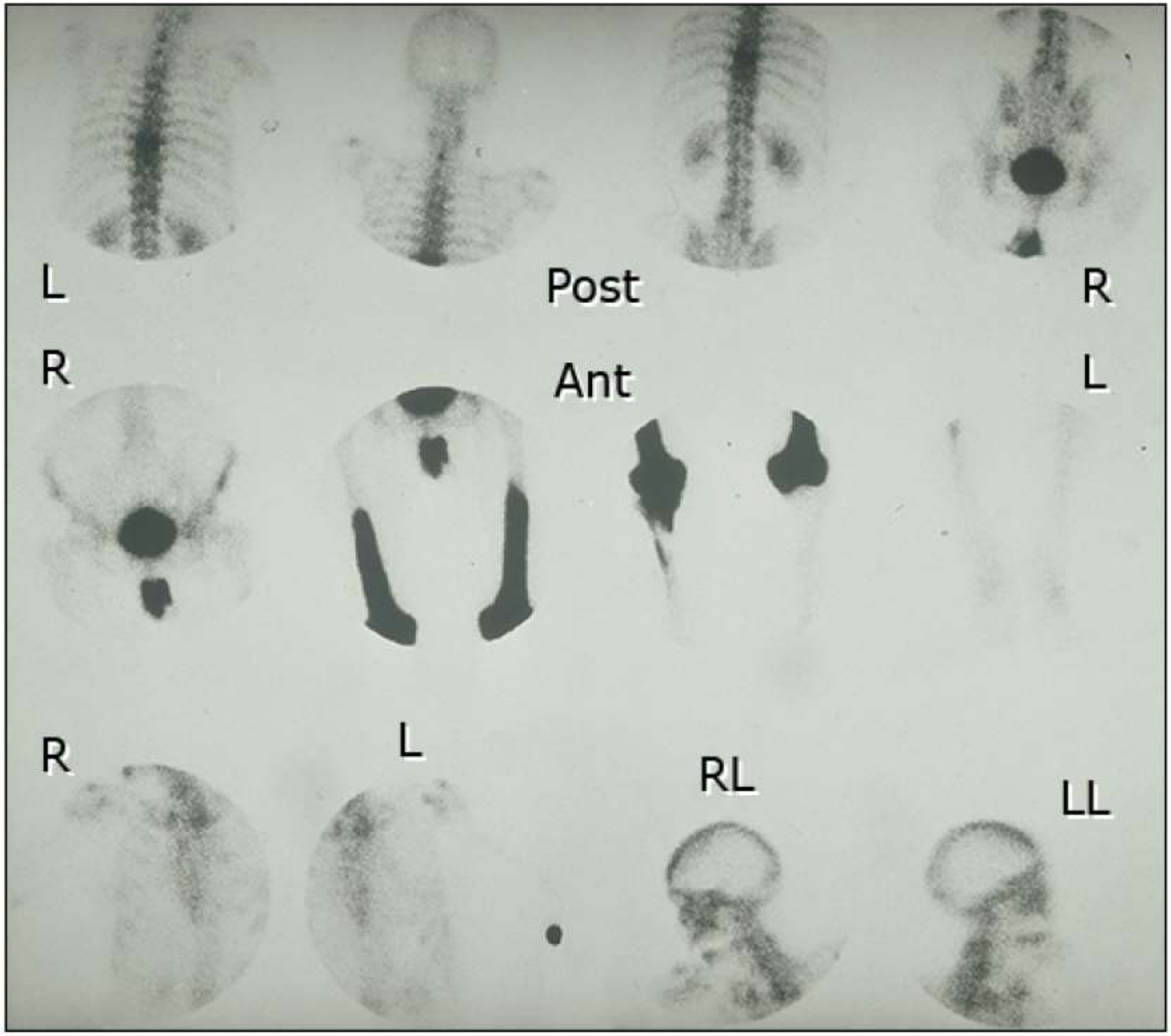
This is a radiograph of the left femur. Note the advancing lytic lesion, the thickening of the femoral diaphysis, and the grossly abnormal remodeling evident there.

Pagetic tibia



This is a pagetic tibia. Note the thickened cortex, with cortical tunneling by pagetic osteoclasts. Lytic lesions (osteoclast resorption) coupled with blastic lesions (osteoblast bone formation) are causing this abnormal bone remodeling, resulting in deformity and structural impairment of bone. Note sparing of the fibula.

Bone scan of Paget affecting both femurs



Bone scan in a patient with Paget disease affecting both femurs. Note the intense uptake, beginning in subchondral bone and moving in one direction through that bone. There is a suggestion by this bone scan of Paget disease in the R tibia as well.