Osteoporosis:

It is reduced bone density, which causes micro-architectural deterioration of bone tissue and leads to an increased risk of fracture.

Bone mass increases during growth to reach a peak between the ages of 20 and about 45 years, but falls thereafter in both genders. The reduction in bone formation is thought to be partly due to differentiation of bone marrow stem cells to adipocytes, as opposed to osteoblasts.

Osteoporosis sometimes occurs because of failure to attain adequate levels of peak bone mass but is more commonly due to age-related bone loss.

Bone resorption is rapid, and a resorption pit is formed within 10 to 14 days. Bone formation can take up to 3 or 4 month.

Two proteins that influence osteoclast activity have been identified: osteoprotegerin (OPG) and RANKL, which are produced by osteoblasts.8 Estrogen deficiency increases osteoblast production of RANKL, which stimulates maturation and activity of osteoclasts.

Genetic factors account for up to 80% of variation in bone density. Environmental factors, such as exercise and calcium intake during growth and adolescence, are important in maximising peak bone mass and in regulating rates of post-menopausal bone loss. Smoking has a detrimental effect on BMD and is associated with an increased fracture risk, partly because female smokers have an earlier menopause than non-smokers. Heavy alcohol intake is a recognised cause of osteoporosis and fractures but moderate intake does not substantially alter risk.

Idiopathic osteoporosis age-related osteoporosis or osteoporosis associated with inheritance of genetic variants that regulate bone density.

Secondary osteoporosis

Osteoporosis can occur in association with a variety of diseases and drug treatments

Endocrine disease

· Hypogonadism

· Hyperthyroidism

· Hyperparathyroidism

· Cushing’ s syndrome

Inflammatory disease

· Inflammatory bowel disease

· Ankylosing spondylitis

· Rheumatoid arthritis

Drugs

· Glucocorticoids

· Gonadotrophin-releasing hormone (GnRH) agonists

· Levothyroxine over-replacement

· Aromatase inhibitors

· Alcohol intake > 3 U/day

· Heparin

Gastrointestinal disease

· Malabsorption · Chronic liver disease

Lung disease

· Chronic obstructive pulmonary disease

Miscellaneous

· Anorexia nervosa

· Highly trained athletes

· Immobilisation

· Body mass index < 18

Glucocorticoid-induced osteoporosis

The risk of osteoporosis is related to dose and duration of glucocorticoid therapy and increases substantially in patients who have taken more than 7.5 mg of prednisolone daily for more than 3 months. Glucocorticoids mainly cause osteoporosis by inhibiting bone

formation and causing apoptosis of osteoblasts and osteocytes. Other contributory mechanisms include inhibition of intestinal calcium absorption, increased renal excretion of calcium

Clinical features

Osteoporosis does not cause symptoms until a fracture occurs. The term ‘fragility fracture’ is used to describe a fracture that occurs as the result of a fall from standing height or less.

In hip fracture, the patient is (with rare exceptions) unable to weight-bear and has a shortened and externally rotated limb on the affected side. The presentation of vertebral fractures is variable. Some patients present with acute severe back pain. This may radiate to the anterior chest or abdominal wall. In others the presentation is with height loss and kyphosis in the absence of pain or with chronic back pain.

Investigations:

Osteoporosis is characterized by normal serum levels of calcium, phosphate, and alkaline phosphatase.

25% to 50% of bone mass must be lost to show osteopenia on radiographs.

The most important investigation is DXA at the lumbar spine and hip.

Z-score, the number of standard deviations above or below the mean for the patient's age, sex and ethnicity. This value is used in premenopausal women, men under the age of 50, and in children.

T-score, the number of standard deviations above or below the mean for a healthy 30-year-old adult of the same sex and ethnicity as the patient

The World Health Organization has published criteria for osteoporosis on the basis of bone density:

• Normal bone density if the T-score is greater than −1.

• Osteopenia (low bone mass) is defined as a bone density measurement between 1 and 2.5 SD below the young adult mean (T-score between −1 and −2.5).

• Osteoporosis is defined as a bone density measurement less than 2.5 SD below that of young, healthy control subjects (T-score <2.5).

Clinical Indications for Bone Densitometry

- All post-menopausal women <65 yr who have one or more additional risk factors for osteoporosis (besides menopause)
- All women >65 yr regardless of additional risk factors
- To document reduced bone density in patients with vertebral abnormalities or osteopenia on radiographs
- to monitor the efficacy of a therapeutic intervention or interventions for osteoporosis
- To diagnose low bone mass in people treated with glucocorticoids

Management

The aim of treatment is to reduce the risk of fracture.

Optimization of Ca and vitamin D intake.

Calcitonin: Patients treated with parenteral or intranasal calcitonin may also obtain a beneficial analgesic response in the presence of osteoporotic fractures.

Antiresorptive therapy:

Bisphosphonates are the first-line treatment for osteoporosis. The bisphosphonate is released within the osteoclasts and impairs bone resorption.

Bisphosphonates reduce the risk of fracture in patients with osteoporosis but do not completely prevent fractures occurring.

Oral bisphosphonates are typically given for a period of 5 years. If patients have remained free of fractures after 5 years and if BMD levels have increased and no longer remain in the osteoporotic range, it is usual to instigate a 5-year spell off therapy.

A change in treatment should be considered in patients who have lost BMD despite oral bisphosphonates.

With intravenous zoledronic acid annually , for 3 years of therapy.

Oral bisphosphonates are poorly absorbed from the gastrointestinal tract and should be taken on an empty stomach with plain water; no food should be eaten for 30–45 minutes after administration

Adverse effects of bisphosphonates

Common

• Upper gastrointestinal intolerance (oral)

• Acute phase response (intravenous)

Less common

• Atrial fibrillation (intravenous zoledronic acid)

• Hypocalcaemia (intravenous bisphosphonates)

• Atypical subtrochanteric fractures

They are contraindicated in patients with oesophageal stricture or achalasia, since tablets may stick in the oesophagus, causing ulceration and perforation.

Osteonecrosis of the jaw is characterised by the presence of necrotic bone in the mandible or maxilla, typically occurring after tooth extraction.

Denosumab is a monoclonal antibody that inhibits bone resorption by neutralising the effects of RANKL. It is administered by subcutaneous injection.

One potential adverse effect is hypocalcaemia but this can be mitigated by calcium and vitamin D supplements.

Denosumab may rarely cause osteonecrosis of the jaw.

Hormone replacement therapy: Cyclical HRT with oestrogen and progestogen prevents post-menopausal bone loss and reduces the risk of vertebral and non-vertebral fractures in postmenopausal women. It is not recommended above the age of 60 because the risk of an increased risk of breast cancer, cardiovascular disease and venous thromboembolic disease.

Raloxifene is a selective oestrogen receptor modulator (SERM) that acts as a partial agonist at oestrogen receptors in bone and liver, but as an antagonist in breast and endometrium.

It is effective in reducing the risk of vertebral fractures but does not influence the risk of non-vertebral fracture.

Anabolic therapy:

Teriparatide is the 1-34 fragment of human PTH. It is an effective treatment for osteoporosis, which works by stimulating new bone formation. It is given by a self-administered subcutaneous injection daily for 2 years

Mild hypercalcaemia may occur but it is usually asymptomatic and does not require discontinuation of treatment.

Weight-bearing exercise increases muscle strength and may stabilize or modestly increase bone density

Surgery

Orthopaedic surgery with internal fixation is frequently required to reduce and stabilise osteoporotic fractures

Vertebroplasty is sometimes used in the treatment of painful vertebral compression fractures.

Vitamin D deficiency

- Classical Lack of sunlight exposure (dark-skinned individuals produce less vitamin D in response to sunlight) and poor diet (the diet of exclusively breastfed infants and of partially formula-fed infants does not provide the recommended intake of vitamin D).
- Gastrointestinal disease: Malabsorption
- Failure of 1,25 vitamin D synthesis
  - Chronic liver disease
  - Chronic renal failure: kidney damage Impaired conversion of 25(OH)D3 to 1,25(OH)2D3
  - Vitamin D-resistant rickets type I (autosomal recessive)
- Vitamin D receptor defects: Vitamin D-resistant rickets type II (autosomal recessive)
- Defects in phosphate and pyrophosphate metabolism
  - Hypophosphataemic rickets
  - Hypophosphatasia: deficiency of alkaline phosphatase
- Iatrogenic and other causes
  - Aluminium Use in dialysis
  - Fluoride High fluoride in water Inhibition of mineralisation by fluoride

Clinical features

Vitamin D deficiency does not cause symptoms and the diagnosis is made as the result of biochemical testing. If vitamin D deficiency is prolonged and severe, then osteomalacia and rickets will develop.

The diagnosis can be made by measurement of serum 25(OH)D. In patients with low 25(OH)D, measurements of PTH, serum calcium, phosphate and ALP should also be considered.

If low 25(OH)D levels are combined with raised levels of PTH, this is of more significance since it indicates secondary hyperparathyroidism. Serum ALP, calcium and phosphate levels are normal in uncomplicated vitamin D deficiency.

Osteomalacia and rickets

Pathogenesis

Osteomalacia and rickets occur as the result of chronic secondary hyperparathyroidism, which invariably accompanies severe and long-standing vitamin D deficiency. The sustained elevation in PTH levels maintains normal levels of serum calcium by increasing bone resorption, which eventually causes progressive demineralisation of the skeleton. The under-mineralised bone is soft, mechanically weak and subject to fractures, particularly stress fractures. Normal levels of serum calcium tend to be maintained until a very advanced stage, when hypocalcaemia may occur.

Clinical features

Vitamin D deficiency in children causes:

Delayed development

Muscle hypotonia

Craniotabes (small unossified areas in membranous bones of the skull that yield to finger pressure with a cracking feeling), bossing of the frontal and parietal bones and delayed anterior fontanelle closure

Enlargement of epiphyses at the lower end of the radius

Swelling of the rib costochondral junctions (‘rickety rosary’) (Harrison’s grooves).

Osteomalacia in adults can present with fractures and low BMD, mimicking osteoporosis. Other symptoms include bone pain and general malaise. Proximal muscle weakness is prominent and the patient may walk with a waddling gait

Investigations

The diagnosis can usually be made by measurement of serum 25(OH)D, PTH, calcium, phosphate and ALP. Typically, serum ALP levels are raised, 25(OH)D levels are

undetectable and PTH is markedly elevated. Serum phosphate levels tend to be low but serum calcium is usually normal. 1,25-Dihydroxyvitamin D levels (e.g., renal insufficiency and vitamin D–resistant osteomalacia or rickets.

X ray in children show widening and cupping of the metaphyseal regions, Bowing of long bones.

X-rays in adult often show osteopenia or vertebral crush fractures and, with more advanced disease, focal radiolucent areas (pseudofractures or Looser's zones) may be seen in ribs, pelvis and long bones. protrusio acetabula.

Patients with osteomalacia due to vitamin D deficiency may have markedly reduced spine, hip, and forearm BMD. In such patients, treatment with bisphosphonates, teriparatide, or other osteoporosis medications is not appropriate and may exacerbate hypocalcemia.

Where there is doubt, the diagnosis can be confirmed by bone biopsy

Treatment:

All patients should maintain a calcium intake of at least 1000 mg per day since inadequate intake of calcium may contribute to the development of osteomalacia, A higher calcium dose (up to 4 g/day) may be necessary in patients with malabsorption.

For patients with severe vitamin D deficiency (25[OH]D <10 ng/mL), one common approach is to treat with 50,000 international units of vitamin D2 or D3 orally once per week for six to eight weeks, and then 800 international units of vitamin D3 daily thereafter.

For individuals with serum vitamin D levels of 10 to 20 ng/mL, initial supplementation with 800 to 1000 international units daily, For individuals with serum 25(OH)D levels of 20 to 30 ng/mL, initial supplementation with 600 to 800 units of vitamin D3 daily.

Treatment of rickets: 1000-6000 IU/day for 3 months, followed by maintenance dose.

In malabsorptive states, oral dosing and duration of treatment depend upon the vitamin D absorptive capacity of the individual patient. Doses of vitamin D of 10,000 to 50,000 international units daily may be necessary to replete patients with gastric bypass or malabsorption.

In liver disease, the vitamin D metabolite Calcitriol (1,25-dihydroxyvitamin D)

In renal disease, 1alpha-hydroxyvitamin D. It requires hepatic 25-hydroxylation prior to becoming therapeutically active.

The recommended intake of vitamin D to prevent deficiency is:

400 international units daily in healthy infants.

600 int. units daily for children 1 to 18 years

600-800 IU daily for age >18yrs

Read more in:

- Up to date 2018
- Davidson's Principles and Practice of Medicine, 23rd edition
- Kelley & Firestein's Textbook of Rheumatology, 10th edition