CONGENITAL DISEASE OF BONE
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Etiology

• Congenital diseases of bone is malformations to hereditary disorders associated with abnormalities affecting the entire skeletal system.

• Developmental anomalies resulting from localized problems in the migration of mesenchymal cells and formation of condensations are called dysostoses.

• They are usually result from (1) limited to an embryologic structures and (2) mutations in specific genes.
Etiology

• The more common lesions include (1) **aplasia** (e.g., congenital absence of a digit or rib), (2) formation of *extra bones* of digits or ribs, and (3) abnormal *fusion of bones* (e.g., premature closure of the cranial sutures or congenital fusion of the ribs).

• Mutations that interfere with *bone* or *cartilage growth* and/or normal *matrix components* (e.g. affecting growth factors or their receptors) called **dysplasias**.
Skeletal Dysplasias
(1) Solid bone matrix,
(2) Weakened bone matrix
Osteogenesis Imperfecta

- Osteogenesis imperfecta (OI), also known as "brittle bone disease", is actually a group of hereditary disorders caused by defective synthesis of type I collagen.

- Because type I collagen is a major component of (1) extracellular matrix in other parts of the body, (2) numerous extra-skeletal manifestations (affecting e.g., skin, joints, and eyes).

- The fundamental abnormality in all forms of OI is too little bone, resulting in extreme skeletal fragility.
Bone Imperfecta
Osteogenesis Imperfecta

- The type I OI have a
  (1) normal lifespan,
  (2) increased proclivity to
  fractures during childhood
  but decreasing in frequency
  after puberty.

- The type II OI is uniformly
  fatal pre- or immediately
  post-partum due to multiple
  fractures that occur in utero.

- Classic finding in type I OI
  (1) blue sclerae (decreased
  scleral collagen content),
  (2) hearing loss can be related
  to conduction defects in the
  middle and inner ear bones,
  (3) small misshapen teeth are a
  result of dentin deficiency.
Osteogenesis imperfecta
The classic blue sclerae of a person with osteogenesis imperfecta
Achondroplasia

- Achondroplasia is a major cause of *dwarfism*. The underlying etiology is a point mutation in the *fibroblast* growth factor receptor 3 (FGFR3).

- Abnormalities in
  (1) chest development and
  (2) death from respiratory failure soon after birth.

- *Note:* is a type of cell that synthesizes the extracellular matrix and collagen.
Achondroplasia
Genetic Mutation, dwarfism

Achondroplasia
Achondroplasia
Achondroplasia

- The most conspicuous changes include marked, disproportionate shortening of the proximal extremities, bowing of the legs, and a lordotic (弯腰) posture.
- The cartilage growth plates are disorganized and hypoplastic.
Achrondroplasia

**Dwarfism** is a medical or genetic condition that usually results in an adult height of four feet ten or shorter, among both men and women, although in some cases a person with a dwarfing condition may be slightly taller than that. By far the most frequently diagnosed cause of short stature is achondroplasia, a genetic condition that results in disproportionately short arms and legs. The average height of adults with achondroplasia is four feet.
Osteopetrosis

**Osteopetrosis:** is a condition present at birth (congenital) which the bones are overly dense. This results from an imbalance between the formation of bone and the breakdown of the bone. There are three types of osteopetrosis of varying severity. Symptoms can include fractures, frequent infections, blindness, deafness, and strokes.
Osteopetrosis
Osteopetrosis
Osteopetrosis

• Besides fractures, patients with osteopetrosis frequently (1) have cranial nerve problems (due to compression from surrounding bone), and (2) recurrent infections (attributable to diminished hematopoiesis resulting from reduced marrow space). (3) often develop hepatosplenomegaly due to expansive extra-medullary hematopoiesis.
ACQUIRED DISEASES OF BONE DEVELOPMENT

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Etiology

• Many nutritional, endocrine, and systemic disorders affect the skeletal system.

• Nutritional deficiencies causing bone disease include deficiencies of
  (1) vitamin C (causes scurvy) and
  (2) vitamin D (involved in calcium uptake; deficiency causes rickets and osteomalacia).
Etiology

• Primary and secondary hyperparathyroidism also cause significant skeletal changes.

• The major focus of the discussion here will be (1) osteoporosis, resulting from a loss of bone mass, & (2) Paget disease, a disease associated with the loss of osteoclast function.
Osteoporosis

• Osteoporosis is a disease characterized by increased porosity of the skeleton resulting reduced bone mass.
• It is associated with an increase in bone fragility and susceptibility to fractures.
• The disorder may be localized to a certain bone or region, as in limb, or may involve the entire skeleton, as a manifestation of a metabolic bone disease.
Osteoporotic vertebral body (*right*) shortened by compression fractures, compared with a normal vertebral body. Note that the osteoporotic vertebra has a characteristic loss of horizontal trabeculae and thickened vertical trabeculae.
Osteoporosis

**Osteoporosis:** which means "porous bones," is a condition that causes bones to gradually thin and weaken, leaving them susceptible to fractures. About 2 million fractures occur each year due to osteoporosis.

The most common forms of osteoporosis are

(1) senile and
(2) postmenopausal osteoporosis;

- Senile osteoporosis affects all aging individuals, while postmenopausal osteoporosis affects only women after menopause.
Osteoporosis

• Peak bone mass is achieved during young adulthood, but beginning in the 30 or 40 years old in both sexes, this age-related bone loss-averaging 0.7% per year-is a normal biological phenomenon.

• Such losses generally occur in the spine and femoral neck, these sites are more prone to fractures in individuals with osteoporosis.
Hip fracture due to osteoporosis
Osteoporosis

Pathogenesis

• In adults there is a dynamic equilibrium between (1) bone formation by osteoblasts, maintenance by osteocytes, and (2) resorption by osteoclasts.
Bone Growth
Rickets and Osteomalacia

• Both rickets and osteomalacia are manifestations of vitamin D deficiency or its abnormal metabolism.

• **Rickets** is a disorder in which a growing infant or child's bones have abnormally low levels of calcium and phosphorus, which causes them to become weak and soft. This can lead to permanent deformities in the skeleton and teeth, a failure to grow properly, muscle weakness, seizures, and chronic pain.

• The fundamental change is defective bone mineralization resulting in overabundant nonmineralized osteoid.
Rickets and Osteomalacia
Rickets and Osteomalacia

Osteomalacia

Rickets
Rickets and Osteomalacia

Signs of rickets:
- bony necklace
- curved bones
- big joints
- bowed legs

SUNLIGHT IS THE BEST PREVENTION AND TREATMENT OF RICKETS
Hyperparathyroidism

• Parathyroid hormone (PTH) plays a central role in Ca^{2+} homeostasis via its effects on:
  (1) increased resorption of Ca^{2+} by the renal tubules
  (2) increased urinary excretion of phosphates
  (3) increased synthesis of active vitamin D_3, by the kidneys, which in turn enhances Ca^{2+} absorption from the gut and
  (4) mobilizes bone Ca^{2+} by inducing RANKL.
Hyperparathyroidism

- **Paracrine mechanisms regulating osteoclast formation and function.**

Osteoclasts are derived from the same stem cells that produce macrophages. RANK (receptor activator for nuclear factor-κB) receptors on osteoclast precursors bind RANK ligand (RANKL) expressed by osteoblasts and marrow stromal cells.

Along with macrophage colony-stimulating factor (M-CSF), the RANK-RANKL interaction drives the differentiation of functional osteoclasts.

Stromal cells also secrete osteoprotegerin (OPG) that acts as a decoy receptor for RANKL, preventing it from binding the RANK receptor on osteoclast precursors.

Consequently OPG prevents bone resorption by inhibiting osteoclast differentiation.
Pathophysiology of postmenopausal and senile osteoporosis

- **Menopause**
  - Decreased serum estrogen
  - Increased IL-1, IL-6, TNF levels
  - Increased expression of RANK, RANKL
  - Increased osteoclast activity

- **Aging**
  - Decreased replicative activity of osteoprogenitor cells
  - Decreased synthetic activity of osteoblasts
  - Decreased biologic activity of matrix-bound growth factors
  - Reduced physical activity
Hyperparathyroidism

• The net result is an elevation in serum Ca$^{2+}$, which, under normal circumstances, inhibits further PTH production.

• However, excessive or inappropriate levels of PTH can result from
  (1) autonomous parathyroid secretion (primary hyperparathyroidism) or
  (2) can occur in the setting of underlying renal disease (secondary hyperparathyroidism).
Hyperparathyroidism

- In chronic renal insufficiency there is inadequate vitamin D$_3$ synthesis that ultimately affects gastrointestinal Ca$^{2+}$ absorption.
- The hyperphosphatemia of renal failure also suppresses renal $\alpha_1$-hydroxylase, further impairing vitamin D synthesis.
- Additional influences include metabolic acidosis and aluminum deposition in bone.
Hyperparathyroidism

- As bone mass decreases, affected patients are increasingly susceptible to (1) fractures, (2) bone deformation, and (3) joint pathology.
- Fortunately, reduction of PTH level can result in complete lesion regression.
**Osteonecrosis (Avascular Necrosis)**

- Mechanisms contributing to bone ischemia include:
  1. Vascular compression or disruption (e.g., following a fracture)
  2. Steroid administration thromboembolic disease (e.g., nitrogen bubbles in caisson disease)
  3. Primary vessel disease (e.g., vasculitis)

- Most cases of bone necrosis are due to fracture or occur after corticosteroid use.

**Clinical Course**

- Symptoms depend on the size and location of injury.
- Subchondral infarcts initially declare with pain during physical activity, becoming more persistent with time.
Osteonecrosis (Avascular Necrosis)

Figure 1: Osteonecrosis of the Jaw Presents As Exposed Necrotic Bone—It is seen in both the maxilla and mandible. Most cases are initiated by a dental extraction (A) but some occur spontaneously (B). The most common areas of spontaneous osteonecrosis of the jaw are areas where the mucosa is thin, such as the lingual posterior mandible.
Osteonecrosis (Avascular Necrosis)
Osteonecrosis (Avascular Necrosis)
Osteonecrosis (Avascular Necrosis)

- Ischemic necrosis with resultant bone infarction occurs relatively frequently.
- Medullary infarcts are usually clinically silent except for large ones (e.g., with Gaucher disease, caisson disease, or sickle cell disease).
- Medullary infarcts are usually stable.
- Subchondral infarcts, often collapse and can lead to severe osteoarthritis.
- Roughly 50,000 joint replacements are performed each year in the USA specifically to treat the consequences of osteonecrosis.
Osteochondroma

• They are relatively common benign cartilage-capped outgrowths attached by a bony stalk to the underlying skeleton.

• Solitary (isolate) osteochondromas are usually first diagnosed in late adolescence and early adulthood (male-to-female ratio of 3 : 1).

• Multiple osteochondromas become apparent during childhood (an autosomal dominant disorder).
Osteochondroma

![Osteochondroma Images]

- Femur (Thighbone)
- Tibia (Shinbone)
- Humerus (Upper Arm Bone)
Osteochondroma
Osteochondroma
Osteochondroma

- Osteochondromas develop arising at the metaphysis near the growth plate of long tubular bones, especially about the knee; they tend to stop growing once the normal growth of the skeleton is completed.

- Occasionally they develop from bones of the pelvis, scapula, and ribs, and in these sites are frequently sessile.

- Rarely, osteochondroma (exostoses) involve the short tubular bones of hands and feet.
Osteochondroma

Clinical Features

• Osteochondromas are slow-growing masses that are painful when they impinge on a nerve or if the stalk is fractured.

• In multiple hereditary exostosis, deformity of the underlying bone suggests an associated disturbance in epiphyseal growth.

• Osteochondromas rarely progress to chondrosarcoma or other sarcoma, although patients with the hereditary syndrome are at increased risk of malignant transformation.

• In many cases, they are detected only incidentally.
Chondroma
The development of an osteochondroma, beginning with an outgrowth from the epiphyseal cartilage.
Chondromas, Tumor of Bone
Chondromas

Clinical Features

• Most en chondromas are detected as incidental findings.

• Occasionally they are (1) painful and (2) cause pathologic fractures.

• Solitary chondromas rarely undergo malignant transformation.
Reference

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