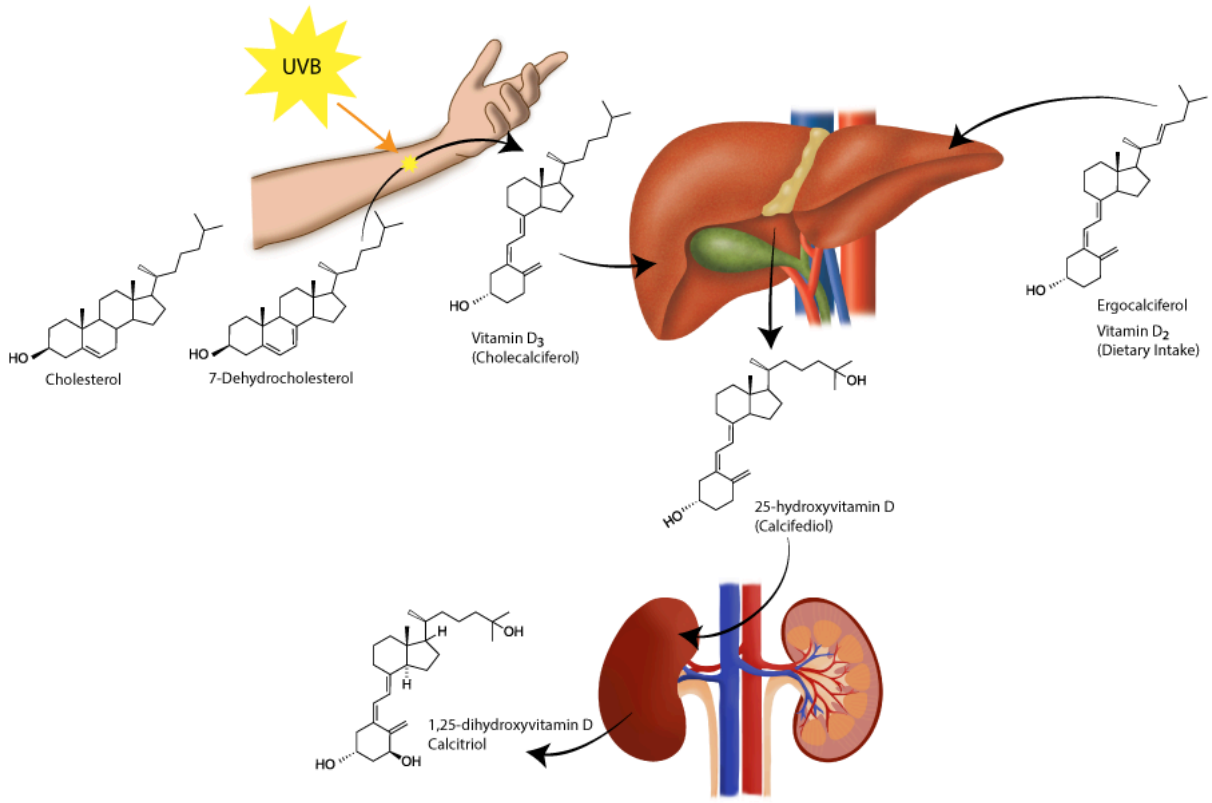
10.1.3

Osteomalacia, Rickets, and Paget's Disease

Osteomalacia and Rickets

While osteoporosis causes a loss of total bone mass (matrix and mineral), osteomalacia and Rickets are both characterized by a selective loss of minerals. **Rickets** is the term used to describe bone softening in the growing bones of children. Clinical features of rickets include enlargement of the ends of long bones, stunted growth, lumbar lordosis (inward curve of lumbar spine, or swayback), and bowing of the legs. **Osteomalacia** literally means softening of bone and is a general term used whenever there is inadequate mineralization of bone in individuals of any age. This means that there will be a greater percent of collagen (unmineralized portion of bone) compared to hydroxyapatite (calcium-containing mineralized portion). Patients with osteomalacia often experience bone pain and tenderness and are at increased risk for fractures, especially in the distal radius and proximal femur.

Vitamin D deficiency is the predominant cause of osteomalacia. Patients with a vitamin D deficiency are at risk for osteomalacia because vitamin D plays an important role in signaling intestinal absorption of calcium, phosphate, and magnesium, all of which are used in bone. Vitamin D receptors are found in most cells of the body and have shown effects on cell growth, differentiation, and immune function. In fact, studies have shown increased incidence of autoimmune susceptibility in vitamin D deficient individuals. Phosphate deficiency can also cause a problem with bone mineralization because phosphate is necessary to make hydroxyapatite.



Vitamin D Cascade *Image by Becky T. BYU-I F19*

To help you better understand how a vitamin D deficiency can contribute to osteomalacia, it is important to consider the biochemistry of vitamin D synthesis within our bodies. The biosynthesis of vitamin D begins in our skin epidermal cells where 7-dehydrocholesterol is made from cholesterol and rapidly converted into cholecalciferol (vitamin D_3) by UVB radiation from sunlight. Cholecalciferol (vitamin D_3) travels in the plasma to the liver where it undergoes enzymatic hydroxylation to become calcifediol (25-hydroxyvitamin D). This molecule then travels to the kidney where another enzymatic hydroxylation occurs to generate calcitriol (1,25-dihydroxyvitamin D), the active form of vitamin D. Note that PTH increases the ability of the kidney to perform the final vitamin D hydroxylation step. Many of our foods, like milk, orange juice, and cereals are fortified with a form of vitamin D. These forms are cholecalciferol (vitamin D_3) or ergocalciferol (vitamin D_2), which is plant-derived and not made by human or animal cells. Like vitamin D_3, vitamin D_2 must be hydroxylated by the liver and then the kidney before becoming active calcitriol.

Understanding the biosynthesis of vitamin D helps us understand the potential causes of vitamin D deficiency. A few are listed below:

1. Intestinal malabsorption can decrease the dietary forms of vitamin D_3 and vitamin D_2.
2. Lack of sunlight to the epidermis can decrease the synthesis of vitamin D_3.
3. Liver or renal failure can diminish the hydroxylation steps required for active vitamin D.
4. Medications like anticonvulsants are known to inhibit the liver from hydroxylating cholecalciferol.

Any of these contributors can cause a vitamin D deficiency and lead to osteomalacia. The risk of developing osteomalacia is the highest for individuals who don't get enough vitamin D in their diet and have little sun exposure, such as the elderly or those who are housebound or hospitalized.

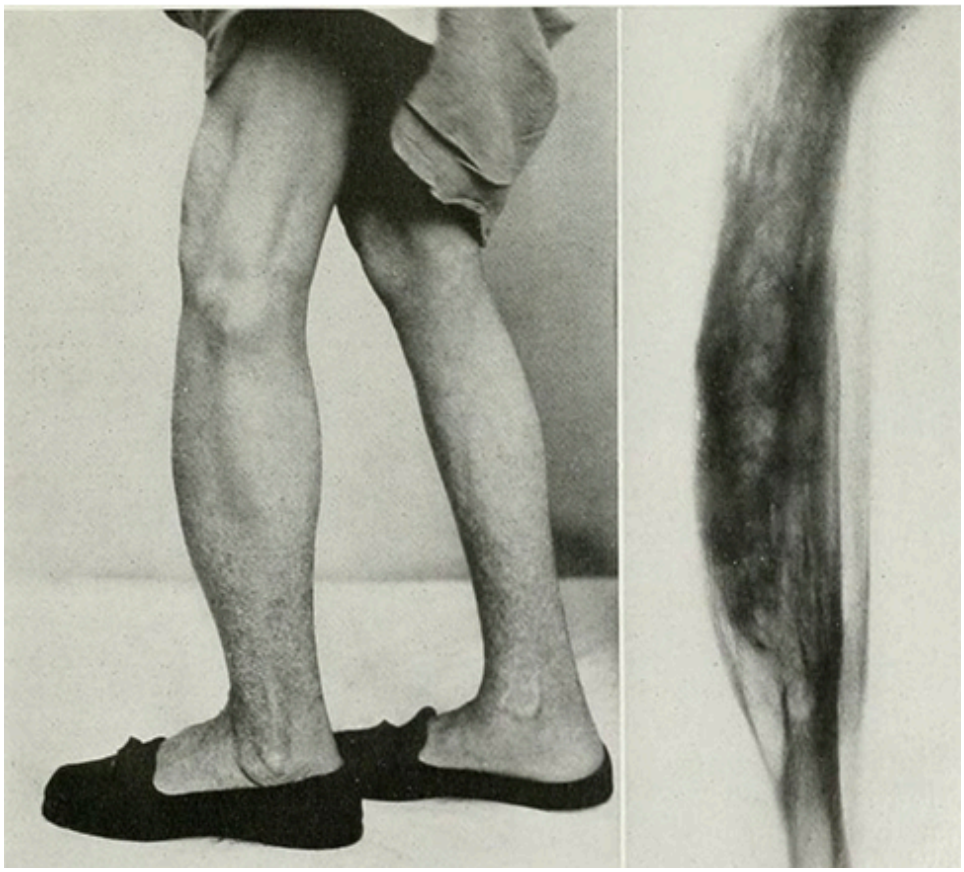
Paget's Disease

Paget's Disease (pronounced PAJ-its) is a chronic condition of dysregulated bone formation and resorption. Recall that healthy bone tissue is constantly undergoing resorption and formation in a balanced and controlled manner to ensure

the skeleton can withstand the forces placed on the joints and limbs. In Paget's disease, genetic mutations and environmental factors affecting the regulatory signals for bone turnover (including the RANK pathway mentioned earlier) result in excessive bone formation and deformities. The dysfunctional regulation typically proceeds with an aggressive increase in osteoclast activity followed by a compensatory, and perhaps greater increase in osteoblast activity. The resulting bone growth is not as strong as healthy bone since its composition is woven bone, not the stronger, more organized lamellar bone. In time, the bone marrow begins to be replaced with fibrous connective tissue and angiogenesis (development of new blood vessels) increases. This causes the bone to be more dense, although not in the correct composition of hydroxyapatite and collagen fibers. Most patients don't experience pain, but if they do it is usually bone pain.

Bone deformities can arise over time as the bones become misshapen and fragile, especially those of the skull, spine, pelvis, and legs. The axial skeleton is usually the most affected and the proximal femur and tibia may become involved as the disease progresses. Deafness can occur if the affected bones are in the skull close to the auditory structures. Patients with Paget's disease have an increased risk of developing osteosarcoma (bone cancer). Heart failure is a common complication if neovascularization occurs in bones to the extent that the heart has a difficult time maintaining blood flow.

The cause of Paget's disease is not well known. Currently, it is thought that a genetic predisposition can trigger the disease if certain environmental conditions arise. One such condition is thought to be particular viral infections such as the measles and mumps, although this remains controversial. The risk of this disease increases with age and if you have a family history of the disease.



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Paget's Disease: Bone deformity in the tibia where the marrow is filled with increased fibrous and vascular tissue, making the bone more dense.