3.3: Calcium in Mineralized Tissues

The formation of calcified tissue—shells, bone, and teeth—is a very complex process that is under strict regulatory control. Despite the obvious importance of this field, relatively little research has been directed toward elucidation of the underlying mechanisms, perhaps because the field spans a broad range of subjects, from inorganic solution and solid-state chemistry to cellular physiology.[155]

Historically, it was long held that formation of biological minerals such as bone was simply the nucleation and growth of calcium hydroxyapatite within an extracellular matrix of collagen. Many proteins other than collagen have now been discovered in appreciable quantities in bone and other biological minerals. It is also apparent that the pattern of calcification differs in shells, bone, teeth, and other mineralized tissues; so it is not likely that there is only one underlying mechanism. Considering the immensity of the subject, we will here only make a few brief comments, mainly about bone and teeth.

As was briefly mentioned earlier in this chapter, the inorganic matter of bone and teeth in many ways resembles apatite minerals ($Ca_5(OH)(PO_4)_3$). Table 3.5 summarizes inorganic solid components of other biominerals.

Table 3.5 - A summary of the main inorganic solid component[8] of the most-common biominerals in living systems.[148]

a) Most real biominerals are actually nonstoichiometric, and contain a number of additional cations (e. g., Mg^{2+}) or anions (e.g., F^-). In addition, the inorganic phase may be interpenetrated by a biopolymer.

Anion	Formula	Crystal Form	Occurrence	Main Function
Carbonate	$CaCO_3$	Calcite Aragonite Valerite	Sea corals, molluscs, and many animals and plants	Exoskeleton; Ca-store; eye lens
Oxalate	$Ca(COO)_2•H_2O$ $Ca(COO)_2•2H_2O$	Whewellite Weddelite	Insect eggs; vertebrate stones	Deterrent; cytoskeleton; Ca store
Phosphate	$(Ca)_{10}(PO_4)_6(OH)_2$ (unit cell comp.)	Hydroxyapatite	Bones; teeth; shells; intracellular in some bacteria	Skeletal; Ca storage; pressure-transducer (piezo-electric)
Sulfate	$CaSO_4•H_2O$	Gypsum	Jelly fish; plants	Gravity device; S and Ca store

A detailed analysis[156] shows that, apart from Ca^{2+} and PO_4^{3-}, many other cations and anions occur in bone, e.g., Mg^{2+}, Na^+, K^+, Sr^{2+}, CO_3^{2-}, F^-, Cl^-, and citrate. X-ray diffraction patterns and electron-microscope pictures of bone show that the inorganic phase is made up of many very small and imperfect crystals. By contrast, dental enamel is made up of much larger and uniform thin crystals. Although the solubility product of calcium hydroxyapatite (see Section II) is such that the equilibrium Ca^{2+} concentration should be in the low micromolar range, bone mineral appears to be in equilibrium with much higher Ca^{2+} concentrations (0.8-1.0 mM).[157] This discussion brings us to the question of how the inorganic crystallites are formed. Obviously both Ca^{2+} and PO_4^{3-} ions must be concentrated in cells or organelles bordering on the regions where mineralization is to take place. Fresh layers of bone matrix are formed by a continuously replenished layer of cells called *osteoblasts* (Figure 3.32A), which, in addition to apatite crystallites, also secrete collagen, and large specific proteins called *osteonectin*, *osteocalcin* (a Gla protein), proteoglycans, and phosphoproteins. In tissues undergoing rapid mineral deposition, the crystallites appear to be formed in vesicles that may have peeled off from the adjacent cell layers. These vesicles seem able to concentrate calcium and phosphate in a manner not well understood.

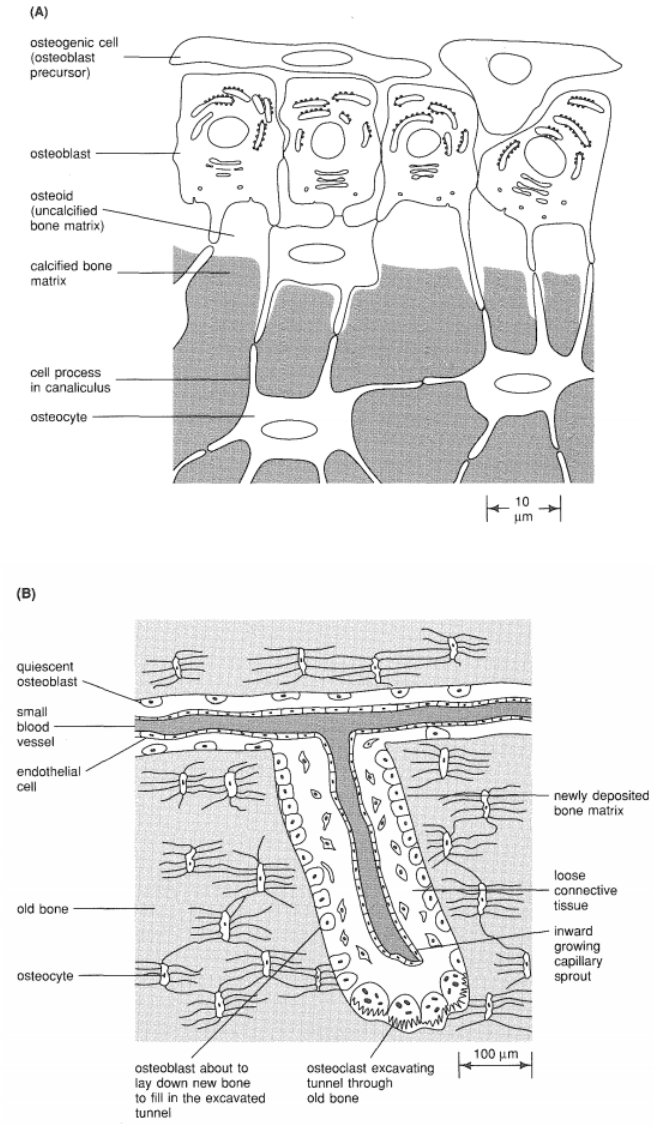

Figure 3.32 - Schematic diagram depicting the roles of the most important cell types in bone formation. (A) The osteoblast cells line the bone surface and secrete the inorganic and organic components (collagen, etc.) that will form new bone. Some osteoblast cells gradually become embedded in their own secretion. A particular secreted bone-specific protein, osteonectin, forms strong links between calcium hydroxyapatite and collagen. The bone-forming cells that become trapped in the bone matrix are now called osteocytes. (B) The osteoclast cells function to remodel compact bone. A group of cells acting together excavate a tunnel through old bone at a rate of about 50 μm per day. Behind the advancing osteoclasts follow a contingent of osteoblasts that line the wall of the tunnel and start to form new bone. Concurrently a capillary vessel is formed along the center of the tunnel and provides the cells with nutrients. Eventually the tunnel will become filled with concentric layers of new bone with only a narrow canal remaining. It is apparent that bone is far from a dull inorganic deposit, and very much a site of continuous activity. It is estimated that 5 to 10 percent of the bone in an adult mammal is replaced per year. Adapted from Reference 159.

Bone, unlike diamond, is not forever. It can be remodeled and dissolved. A serious medical problem, which affects some women after menopause, is **osteoporosis**, i.e., the decalcification of bone. This loss of bone mass, which occurs with increasing age, makes bones more susceptible to breaking under stress. About 50 percent of American women, and 25 percent of American men, over 45 years of age are affected by osteoporosis.[158] Whereas osteoblast cells handle bone formation, another type of cells, *osteoclasts*, can erode it (Figure 3.32B). These macrophage-like cells can form deep tunnels in a bone matrix, and the cavities left behind are rapidly invaded by other cells forming blood vessels and new layers of osteoblasts. The *modus operandi* of osteoclast cells is not well understood at present. They may secrete calcium-chelating organic anions, such as citrate, to assist in the solubilization of the bones, as well as extracellular proteases that degrade the organic part of the matrix.