Normal bone physiology, remodelling and its hormonal regulation

Jennifer S Walsh

Abstract

The skeleton has structural and locomotor functions, and is a mineral reservoir. Bone turnover by osteoclasts and osteoblasts is a lifelong process, incorporating growth, modelling and remodelling to repair microdamage and access the mineral reservoir.

Signalling between bone cells is essential for the coordination of these processes. Osteoblasts regulate osteoclast activity through the receptor activator of nuclear factor-κB (RANK)/RANK ligand/osteoprotegerin system, and osteocytes regulate osteoblast activity through sclerostin secretion.

If resorption and formation are balanced there is no net change in bone mass after each cycle, but with ageing and some disease states resorption exceeds formation leading to remodelling imbalance, decreased bone mass and loss of microstructural integrity.

The rate of remodelling is determined by loading and endocrine influences. The most important endocrine regulator of bone turnover is probably oestrogen, but other hormones regulating bone metabolism include insulin-like growth factor-1, parathyroid hormone and gut and adipocyte hormones.

Keywords Bone; bone turnover; hormones; oestrogen; osteoblast; osteoclast; osteocyte

Normal bone physiology

The skeleton has structural, protective and locomotor functions and is a reservoir for calcium.

Cortical bone is heavily calcified and fulfils a mainly structural and protective role. Trabecular bone is less heavily calcified, and has a greater surface area which allows it to be metabolically active. Overall the adult skeleton is about 80% cortical bone and 20% trabecular bone. The proportion of trabecular and cortical bone varies by skeletal site; for example vertebrae are rich in trabecular bone but have very little cortex, but long bones have much thicker cortices and relatively less trabecular bone.

Growth is the process through which bones increase in size and become mineralised during childhood and adolescence. Bone mass increases from approximately 80 g at birth to 3000 g at peak bone mass (at about age 25). Flat bones (such as the skull) grow by intramembranous ossification and long bones (such as the femur and humerus) grow in length by endochondral ossification and in width by periosteal apposition.

Modelling is the process through which bones are shaped and adapt to loading or other influences. Modelling can result in changes in bone mass, size and geometry. Cortical modelling at the periosteal or endosteal surfaces changes bone diameter and cortical thickness.

Remodelling is the continuous process of bone renewal and repair which continues throughout adult life.

Bone turnover is high during bone acquisition and modelling in growth and puberty, then decreases to a nadir at about age 40. There is a rapid increase in turnover in menopausal women, and a more gradual age-related increase in men.

Bone matrix and mineralization

Bone matrix is composed of type I collagen fibres, with glycoproteins, proteoglycans, γ-carboxylated (gla) proteins and water. Many of the non-collagenous proteins have physiological roles in the regulation of bone cell activity or mineralization.

Type I collagen is a triple-helical molecule containing two identical α1 chains and one α2 chain. The collagen fibres in mature bone are orientated in alternating layers which confers maximum strength on the structure (lamellar bone). Bone matrix laid down acutely after fracture healing, or in high turnover states such as Paget's disease is disorganized, without lamellar configuration (woven bone) and is weaker than lamellar bone.

The mineral component of bone tissue is calcium hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). The hydroxyapatite crystals lie along the collagen fibres and within the ground substance. The mineral strengthens the bone by increasing the mechanical resistance of the bone material.

The matrix and mineral components both contribute to the material properties of bone. The collagen matrix provides toughness (the maximum amount of energy bone can absorb before fracture) and the mineral provides stiffness (the extent to which bone resists deformation in response to an applied force). Abnormalities of collagen lead to fracture in osteogenesis imperfecta due to reduced toughness. Under- or over-mineralization can lead to fracture due to loss of stiffness or excess stiffness.

Bone formation and resorption

Bone formation and resorption are the basis of growth, modelling and remodelling.

The bone remodelling cycle is an ongoing process that renews bone to repair microdamage and maintain strength. It also maintains serum calcium in the normal physiological range by release of mineral from the bone matrix as required. About 5−10% of the adult skeleton is replaced by remodelling each year.

On trabecular bone and at the endocortical surface, remodelling takes place on the surface of bone, but within cortical bone the osteoclasts form a cutting cone through the bone matrix.

The signal to initiate remodelling may be endocrine (such as increased parathyroid hormone (PTH) in response to hypocalcaemia), which leads to generalized increases in osteoclast activation. Localized remodelling is initiated in response to microdamage, probably by signals from osteocytes.

During a remodelling cycle, osteoclasts on the bone surface become activated and resorb bone matrix, creating a defect which is filled in by osteoblasts. The cycle usually takes about 200 days to complete. The bone remodelling cycle is highly regulated, and resorption and formation are closely coupled, so that in health and under normal conditions bone formation will

Jennifer S Walsh *PhD FRCP FHEA is Senior Clinical Lecturer in the Academic Unit of Bone Metabolism at the University of Sheffield, UK. Conflicts of interest: none declared.*

equal resorption, and the amount of bone tissue will be the same at the beginning and end of the cycle (Figure 1).

Osteoclasts are giant multinucleated cells of monocyte lineage. They attach to bone with integrins, and their ruffled border forms a sealed compartment over the bone surface. They secrete hydrogen ions and enzymes such as cathepsin K and matrix metalloproteases (MMPs) into the sealed compartment. The acidification dissolves the bone mineral and the enzymes break down the matrix. Osteoclast differentiation, activation and apoptosis are subject to multiple local and endocrine influences. The critical factors in osteoclast differentiation are macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-κB (RANK) ligand. Anti-resorptive treatments for osteoporosis (including bisphosphonates, hormone replacement, selective oestrogen receptor modulators and denosumab) decrease osteoclast activity and so slow remodelling. Bisphosphonates attach to the bone surface and are internalised by the osteoclast during bone resorption, disabling the osteoclast or inducing apoptosis. Denosumab is a monoclonal antibody against RANK ligand. The most recent anti-resorptive drugs to be developed are cathepsin K inhibitors, although they are not yet licensed.

Osteoblasts generate bone matrix and facilitate mineralisation. They are derived from mesenchymal stem cells, and share a common lineage with chondrocytes, myoblasts, fibroblasts and adipocytes. Quiescent osteoblasts are seen as lining cells along the bone surfaces, and active osteoblasts are seen as a single layer of cuboidal cells on the surface of newly formed osteoid. Osteoblast differentiation is dependent on Runx2, and bone morphogenic proteins (BMPs) are important in the regulation of osteoblastogenesis and stimulation of bone matrix formation. In recent years Wnt signalling has been recognized as a fundamental regulator of osteoblast function. Wnt is a co-receptor with LRP-5, and Wnt signalling is transduced through β-catenin to induce gene expression and drive bone formation. New bone anabolic agents for osteoporosis that target Wnt signalling are in development, such as inhibitors of DKK and sclerostin.

Primary mineralization by deposition of hydroxyapatite crystals begins about 2 weeks after unmineralized matrix (osteoid) is laid down by the osteoblast and continues for about 6 months. Secondary mineralization progresses over 2–3 years, with incorporation of more mineral and development of crystal structures.

When remodelling and bone formation is complete, some osteoblasts undergo apoptosis, some become lining cells and some become trapped in the mineralized bone where they remain as osteocytes.

Bone remodelling has a circadian rhythm, which is more exaggerated for resorption than formation. Bone resorption rises at night and decreases during the day. The rhythm is driven by a combination of endocrine factors (which may include cortisol, oxytocin and melatonin), local factors (such as peroxisome proliferator-activated receptor γ) and clock genes.

Biochemical markers of bone turnover: appreciation of the fundamental importance of the rate and balance of bone remodelling in bone health and disease led to the development of biochemical markers of bone turnover. These markers are products of or factors in bone resorption or formation that can be measured in blood or urine to give an indication of cellular activity. For example, CTX and NTX are commonly used resorption markers derived from components of collagen released when bone matrix is broken down. PINP is a component of procollagen which is cleaved when type I collagen is laid down by osteoblasts, and so is used as a formation marker.

Confirmation of high bone turnover is useful in the diagnosis of metabolic bone diseases, and change in markers can be used to monitor response to treatment.

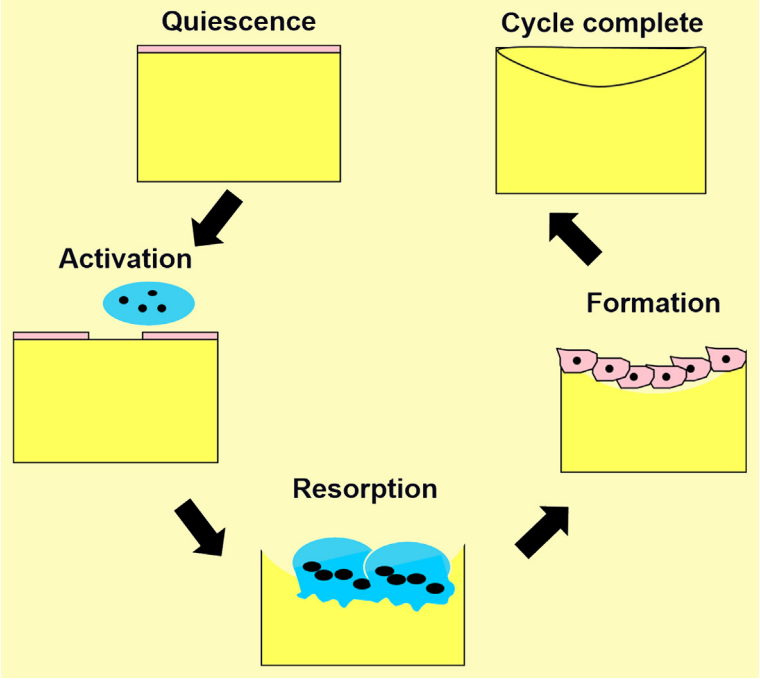

Figure 1 Bone remodelling cycle.