(i) Bone — the tissue we work with

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Abstract

There are two basic processes of bone formation — intramembranous and endochondral, which give rise to the flat bones and long bones respectively. Embryological development and subsequent modelling gives rise to an immensely strong composite tissue with organic and inorganic elements organized superbly for form and function. Far from being a static 'skeleton' built to last a lifetime, all bones are active metabolically, being constantly turned over and playing a crucial role in calcium metabolism. Furthermore it is a tissue that reacts to external applied forces, growing structurally stronger in response to increased loading over time but thinning or dismantling when not needed so that each bone is sufficient for the environment in which it operates — not too big and strong and not too thin and weak.

Keywords bone; bone morphogenetic proteins; calcium homoeostasis; remodelling

Introduction

Bone is a remarkable tissue. Its structure is efficiently suited to its functions of support, protection and calcium storage but the detail is capable of change throughout life in response to environmental changes. Furthermore it is the only tissue in the body capable of healing without scar tissue, but with histologically normal bone tissue, restoring all of the functions of the injured segment. We will therefore explore the basics of that part of human anatomy and physiology that in large part creates and consumes the working life of orthopaedic and trauma surgeons.

Embryology

The development of bone in the growing foetus occurs in two ways, giving rise to flat bones (such as the calvaria of the skull but also the clavicle) or to the long bones.

The development of a flat bone begins with condensation of mesenchyme in a genetically determined pattern and, within this primitive fibrous connective tissue, cellular proliferation occurs. Cells enlarge and, between these cells, collagen is laid down to form the first crude outline of the bone, including its cortical and trabecular zones. Changes in the saccharide composition of the matrix herald mineralisation of this tissue and the emergence of the bone as we would recognize it. However, considerable modelling and remodelling occurs with foetal growth (and onwards through childhood) before the adult form is reached. The processes of bone formation and modelling in the embryo are the same as those that determine bone growth and adaptation, fracture healing and remodelling in the adult[1] and will be discussed further both in this article and in other parts of this minisymposium. The formation of the flat bones involves only fibrous and bone-forming tissues.

The difference in development of long bones begins after condensation of the mesenchyme, when a rod of hyaline cartilage is formed (cartilage anlage) rather than direct mineralisation of the condensate occurring. Within the hyaline rod, at genetically pre-determined sites, a change in the chondrocytes occurs, which gives rise to the ossification centres. The primary centre always appears in the same place in the same bone, usually at the midpoint of the anlage then extending toward each end, producing what becomes the diaphysis of the bone. Within this centre the chondrocytes divide to line up in columns orientated with the long axis of the anlage and they begin to synthesis a matrix rich in Collagen X, which is unique to this site and thought to be required for initial calcification of the matrix. As calcification proceeds then apoptosis of the columns of chondrocytes occurs, leaving acellular columns of calcified cartilage surrounding columnar spaces (lacunae) into which blood vessels begin to grow. Not all of the chondrocytes die, however, some differentiating into osteoblastic phenotypes of the chondroblasts, and this establishes the pattern of central vessels surrounded by the bone tissue which they supply that will be recognisable in a more complex form in adult bone. Later, ossification begins at one or multiple sites towards the ends of the bone — the secondary ossification centres — which form a segment of bone that becomes the epiphysis. The cartilage between the diaphysis and the segment produced by the secondary ossification centre(s) is the epiphyseal line and it is here that continuous division of chondrocytes in the epiphysis produce columns of cells that hypertrophy and die, leaving longitudinal lacunae similar to those that have formed in the diaphyseal region, into which vessels can grow from the adjacent region of the diaphysis. This is the growth plate.

As soon as it is formed, the mineralized matrix of both flat and long bones becomes subject to modelling and remodelling, which starts with osteoclastic/chondroclastic resorption. During embryonic growth this is a highly controlled process involving two groups of genes that control intranuclear gene transcription — the homoeobox (or HOX) genes and the hedgehog genes. One of these — Indian hedgehog, appears critical in chondrocyte and osteoblast differentiation during prenatal bone formation[2] but remains important in the maintenance of the growth plate and normal postnatal growth[3] (mutation of the Indian hedgehog gene is associated with brachydactyly). Interestingly, normal articular cartilage does not have active Indian hedgehog signalling, but it is expressed in the pathological cartilage of osteophytes and can therefore be used as a marker for osteoarthritis, raising the possibility that blockade may offer a treatment inroad. Detailed consideration of the signalling and regulation of bone and cartilage growth and development is outside the scope of this article.

Bone structure

In adult life bones have an outer dense shell (cortex) surrounding a cavity filled with bone marrow and interconnecting bone plates and rods creating a 3D mesh — trabecular bone. Through adult life the trabecular content of the diaphyseal region diminishes and is replaced by adipose tissue, though trabeculae remain

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structurally important and well defined at the ends of the long bones in the metaphyseal/epiphyseal region.

The majority of tissue in the cortex of a long bone is bone matrix, but this forms 20% or less of non-cortical bone. The marrow occupies the spaces between bone plates and columns in trabecular bone and has a haemopoietic component, which has rapid cell turnover producing the various types of blood cell. The remainder is stroma, which is predominantly adipocytes and multipotential stem cells. Although the latter have the potential to form all connective tissue elements, it is believed that in adult life they would normally only differentiate into either osteoblasts or adipocytes.

Although naked eye inspection reveals a distinction between cortical and trabecular bone, microscopic examination shows great histological similarity. Cortical bone can be distinguished into periosteal, Haversian and subcortical layers. The trabecular bone has a mesh-like arrangement of bone plates and columns with run parallel and perpendicular to the axis of the bone, forming braces and struts (Figure 1). Where the cortical bone is thick, such as the adult diaphysis of the femur, the trabeculae may be absent and the marrow cavity filled with fat. Where the cortex is thin, in the metaphysis, the trabeculae are thicker and aligned in the direction of principle forces. The surfaces of the trabecular plates and columns are a site of high bone cell activity.

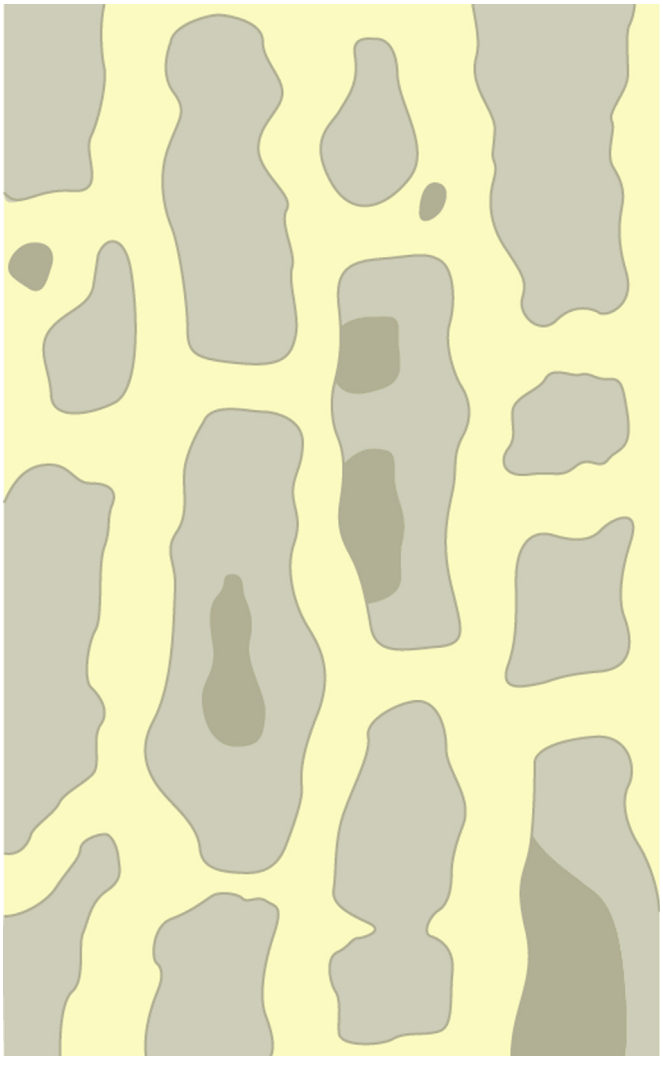

Figure 1 The structure of trabecular bone.

The outer approximately 20% of cortical bone has been laid down by the innermost (cambial) layer of the periosteum and is very close to being completely made of matrix, in which the collagen lamellae run parallel to the surface of the bone. Beneath this is cortical bone formed of intertwining and incomplete cylindrical Haversian systems in which lamellae of collagen are oriented circumferentially around a central canal containing a blood vessel (Figure 2), and this will be discussed in more detail later. At the interface between Haversian and trabecular bone is a distinct layer — subcortical bone — which is characterized by relatively sparse matrix and high cellular activity with active remodelling of the inner cortex.

Like all tissues, bone has a blood supply and a venous drainage, which is a richer network in the periosteum and marrow than in cortical bone, through which neurovascular bundles traverse at a small number of vascular foraminae, which tend to be constant for each bone. A nutrient artery enters each nutrient foramen and divides into ascending and descending branches, which in turn branch to arterioles which contribute to the marrow supply and the Haversian system. In health approximately one third of the (outer) cortex is supplied by the periosteal network and two thirds (inner) by the marrow supply. Trabecular bone has no vessels within the plates and struts of bone, which receive nutritive maintenance from the marrow. Whilst cortical bone is supplied by vessels in Haversian canals, in bones without Haversian systems there are still primary vascular canals, which run both longitudinally and radially.

Haversian systems are the result of remodelling of the mineralized matrix of long bones formed from the condensations of mesenchyme. They are aligned approximately longitudinally but, since the process of remodelling is life-long, the precise arrangement is subject to fluctuation with time. This will be discussed in more detail after we consider the constituents of bone — the matrix and cells.

Matrix

Water accounts for about 20% of the weight of bone matrix; the remainder is mainly three organic and one inorganic components. More than 90% of the organic component is type I collagen.[4] The remainder of the organic component is non-collagenous proteins and non-protein components. The latter include osteocalcin (the most abundant non-collagenous protein,

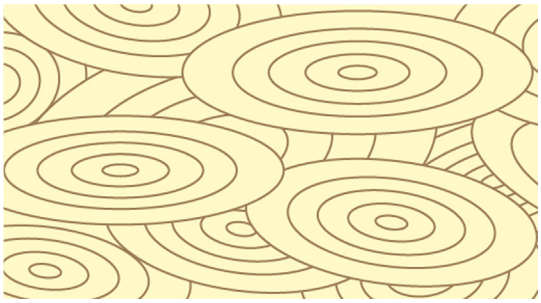

Figure 2 The structure of cortical bone — concentric lamellae surrounding a central canal containing a blood vessel constitute the osteons.