

## Bone metabolism: newer perspectives

ALI NOOR GHANI FRCS

Ampang Putri Specialist Hospital, Kuala Lumpur

### Abstract

The general perception of bone is that of an inert material which provides the framework (skeleton) to **support** the rest of the body and organs. This concept is totally inaccurate. Bone is in fact a vital organ of the body. Structural stability only happens to be one of its many important functions. Bone is a dynamic connective tissue. Among the functions of bone are: (1) support of mechanical loads, (2) protection of vital organ, (3) haematopoiesis, (4) ionized mineral homeostasis, (5) regulation of tissue development, remodeling and repair through the synthesis of paracrine and autocrine factors, and (6) electrical capacitors. Cellular interaction between the 3 cell types and hormonal, physical and chemical signals controls bone health. The osteoblasts appear to communicate with the osteocytes and osteoclasts both directly and indirectly and coordinates cell activity. Mineral metabolism is a well recognised function of bone. However bone biomechanics and electrical function are little appreciated activities of bone.

**Key words:** Bone, metabolism, mineral, homeostasis, skeleton

### INTRODUCTION

The general perception of bone is that of an inert material which provides the framework (skeleton) to support the rest of the body and organs. This concept is totally inaccurate. Bone is in fact a vital organ of the body. Structural stability only happens to be one of its many important functions. Among the functions of bone are:

1. support of mechanical loads,
2. protection of vital organ,
3. haematopoiesis,
4. ionized mineral homeostasis,
5. regulation of tissue development, remodeling and repair through the synthesis of paracrine and **autocrine** factors, and
6. electrical capacitors.

### BONE METABOLISM

#### *Control of bone metabolism*

Bone metabolism is controlled primarily by bone cells. Bone cells respond to various environmental signals **which** include chemical, mechanical, electrical and magnetic. Receptors for these signals are found either on the cell membrane or the cytoplasm. The three bone cell types are osteoblasts, osteoclasts and osteocytes.

Osteoblasts are the bone forming cells and they generally control bone metabolism. Osteoblasts contain the receptors for the majority of the chemical mediators of bone metabolism.

They play a critical role in the regulation of bone activity. Osteoclasts are the **agents** of bone resorption and remodelling. They arise from haematopoietic mononuclear cells. The osteoclasts themselves are multinucleated. Osteocytes are found in the bone matrix in large numbers. Their function is not well understood though recent research indicates that they receive mechanical stimuli and transmit these stimuli to other bone cells.

Osteoblasts and osteocytes develop from the mesenchymal stem cell. These differentiate under the influence of bone morphogenetic protein (BMP). **BMPs** are now recognised as an important means of stimulating bone growth. These cells are in intimate contact with each other via the bone canaliculi. The cells can therefore transmit and receive signals from each other.

Osteoblasts are probably the cells which control the regulation of bone function. They contain the major receptors of bone metabolism and are directly involved in bone synthesis and bone matrix degradation. Osteoid synthesis is carried out by the osteoblasts on the surface of bone. Bone matrix degradation is carried out by resting osteoblasts. These secrete collagenase, collagenase inhibitor and plasminogen activator.

Osteoclasts are multinucleated and are responsible for bone resorption. Osteoclasts have no receptors for the bone resorption **hormones** such as parathyroid hormone, vitamin D and prostaglandin E. Their action is therefore mediated via osteoblasts.

### Cellular interaction

The 3 cell types interact very closely in the control **on** bone metabolism. This process is well illustrated by their response to the hormonal mediators of bone **formation** and resorption. Parathyroid hormone and prostaglandins bind to cell surface receptors on osteoblasts. This activates cyclic AMP production and triggers the calcium messenger system. 1,25-dihydroxy-vitamin D and glucocorticoids diffuse into the cells and bind to intracellular receptors. Intracellular receptors of oestrogen **are** also found in osteoblasts. Through these receptors oestrogen stimulates osteoid formation.

Physical and chemical signals also activate osteoblasts and osteoclasts. Hormonal stimulation of resting osteoblasts results in osteoid being disrupted (as opposed to active osteoblasts). Osteoclasts are then exposed and signals are sent by the osteoblast to activate the osteoclast. Osteoclastic bone resorption then activates specific molecules in the bone matrix such as transforming growth factor beta (**TGF-B**) which stimulates bone formation by osteoblasts or signals osteoclasts to decrease bone resorption.

### Mineral metabolism

Extracellular calcium is important in the regulation of neural, muscular and cardiovascular function and is an intracellular second messenger of most cells. Calcium homeostasis is maintained by three organ systems:-

1. the intestines
2. the bone
3. the **kidneys**

Calcium requirements are high in childhood until the peak bone mass is reached in the third decade of life. Maintenance levels of calcium can only be estimated. However increased amounts of calcium are required in pregnant and lactating women, adolescents and postmenopausal women.

Calcium is critical for the maintenance of membrane electrical potentials, blood coagulation and most functions of living organisms. Calcium levels are maintained within a narrow range and bone calcium is sacrificed to maintain calcium levels in the physiological range.

Bone consists of the inorganic and organic phases. The inorganic phase is calcium hydroxyapatite. The inorganic phase consists of proteins of which 95% is type I collagen. **Amongst** the newly recognised proteins are

**glutamic** acid containing proteins (Gla proteins), bone morphogenetic protein (BMP), and transforming growth factor beta (TGF-B). These proteins have a major role in bone formation and their use in the stimulation of bone healing after fractures and bone surgery is being very actively investigated.

### Endocrine function

Bone is a sensitive organ of the endocrine system. There is a delicate balance between bone and several endocrine organs, including the **skin**, parathyroid glands, liver, kidneys, gonads, adrenals and thyroid. In certain pathological states, the pituitary and **hypothalamus** also affect bone metabolism. One of the primary effects of **all** these endocrine activities is to maintain normal serum calcium levels.

Vitamin D modulates calcium homeostasis directly and indirectly through several calcium regulating cell systems. Generally, approximately half an hour of exposure to ultraviolet light per day on the arms and face is sufficient to provide the minimum amounts of cholecalciferol of approximately 10 mg. The darker the skin the higher the requirement and the converse also applies.

Vitamin D metabolism includes vitamin D<sub>2</sub> from the diet and vitamin D<sub>3</sub> from sunlight. Vitamin D<sub>3</sub> is hydroxylated in the liver into **1,25-dihydroxy-vitamin D<sub>3</sub>**. This is now bound to alpha-globulin. The next step is 1-alpha-hydroxylation in the renal tubular cells to form **1,25-dihydroxy-vitamin D<sub>3</sub>**, the physiologically active form. This step is controlled by the parathyroid hormone.

The major target of **1,25-dihydroxy-vitamin D<sub>3</sub>** are the kidneys, bone and intestines. In the bone **1,25-dihydroxy-vitamin D<sub>3</sub>** affects osteoblasts to control mineralization, bone resorption and cellular differentiation.

### Parathyroid hormone

Parathyroid hormone and vitamin D are the major regulators of calcium and phosphate in the body. The main target organs are the bone, kidneys and the intestines.

Parathyroid hormone causes bone resorption by acting on osteoblasts. These osteoblasts then initiate bone remodelling, resorption and osteoid synthesis. Parathyroid hormone release in turn is controlled by serum calcium levels. In the **kidney**, parathyroid hormone affects the renal uptake of phosphate in the proximal tubules and calcium uptake in the **distal** tubules.

*Calcitonin*

**Calcitonin** is secreted by the C-cells of the thyroid. The main target organs are the bone, kidneys and the intestines. Osteoclastic bone resorption is inhibited. Unlike the other hormones, osteoclasts have receptors for calcitonin.

*Oestrogens and corticosteroids*

Oestrogen receptors exist on osteoblasts. Oestrogen has a direct effect on bone formation and resorption. Corticosteroids cause bone loss by inhibiting calcium absorption, increase renal excretion and indirectly causing secondary hyperparathyroidism.

*Thyroid hormones*

Thyroid hormones in excess lead to bone resorption. Hence hyperthyroidism leads to osteoporosis.

*Bone biomechanics and metabolism*

There is a complex interaction between bone metabolism and biomechanics. Bone is, as we know, important in structural and mechanical function. It is also a reservoir of calcium, phosphate, magnesium, trace elements and a major site of haematopoiesis. Bone is a composite material and is continually undergoing modelling and remodelling. Under normal conditions there is a fine balance of these two processes which safeguards the structural strength of bone, allows rapid repair of injuries to bone and maintains calcium levels.

In pathological states, such as hyperparathyroidism, the control of the remodelling process becomes uncoupled. Bone loss then occurs and this affects mainly the trabecular bone which is found in the vertebrae and around joints.

Bone responds to stress. It has been noted that osteoblasts respond within 24 hours of dynamic loading by increasing their production of RNA. Within a week, **periosteum** becomes active. In dogs, cancellous bone **reponds** to stress within 8 weeks by forming unorganised bone. By 18 to 22 weeks, trabeculae forms within the bone.

Bone stress is therefore essential in the maintenance of bone homeostasis. The weightlessness of space has been shown to cause osteoporosis due to the absence of gravitational stress to the bone. What effect if any osteoporosis

has on the **vascularity** of bone and haematopoiesis has not been well documented.

**CONCLUSION**

Bone is a dynamic tissue which is vital to the survival of most terrestrial organisms. Its role has however not been well documented. For instance, the effect of osteoporosis on the vascularity of bone and haematopoiesis is not known. Suffice to say that bone function is closely linked to many other vital systems of the body. At present, we recognise its great importance in the maintenance of our body structure. We are also **learning** its importance in other functions. Generally it would be wise to realise that weak bone is an indicator of poor health in most other systems of the body.

**SUGGESTED READING**

1. Vaes G. Cellular biology and biochemical mechanism of bone resorption: a review of recent developments on the formation, activation and mode of action of osteoclasts. *Clin Orthop* 1988; 231: 239-71.
2. Eastell R, Riggs BL. Calcium homeostasis and osteoporosis. *Endocrinol Metab Clin North Am* 1987; 16: 829-42.
3. Cormier C. Markers of bone metabolism. *Curr Opin Rheumatol* 1995; 7 (3): 243-8.
4. Joffe P, Ladefoged SD, Cinton C, Jensen LT, Hyldstruo L. Acute effect of oral, intraperitoneal and intravenous 1 alpha-hydroxycholecalciferol on markers of bone metabolism. *Nephrol Dial Transplant* 1994; 9(5): 524-31.
5. Eriksen EF, Colvard DS, Berg NJ, et al. Evidence of oestrogen receptors in normal human osteoblast like cells. *Science* 1988; 241: 84-6.