Metabolic bone disease

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Abstract

The topic of bone metabolism is complex and knowledge of the processes involved, and their control mechanisms, is still evolving. In an article of this size it is inevitable that only a relatively simple account can be given but an understanding of the basic sciences underlying metabolic bone diseases is important for Orthopaedic surgeons. We will explore the normal control mechanisms and the interplay between calcium, phosphate, vitamin D and parathyroid hormone, then discuss the conditions in which normal control is lost.

Keywords calcitonin; calcium metabolism; hyperparathyroidism; osteomalacia; osteoporosis; parathyroid hormone; renal osteodystrophy; vitamin D

Introduction

The topic of Bone metabolism can be explored at several different levels, including genetic, hormonal and end-organ mechanisms.

Under normal circumstances bone is constantly undergoing remodelling and repair, in order to adapt to changing loads and to repair areas of microscopic damage.

A number of metabolic bone diseases can be considered as "side products" of the normal mechanisms that control serum calcium levels. Control of the serum calcium level is vital for cell function, particularly in cells such as the myocardium, so homeostatic mechanisms give priority to maintaining the serum calcium levels within the range required for normal function of such cells. Bone, containing the major body reserve of calcium (99%), is a major, and immediately accessible, source for calcium if the serum concentration drop to potentially dangerous levels. The immediate requirement to maintain adequate serum calcium levels will therefore, in many cases, take priority over the longer term requirements for bone formation and remodelling.

This article will cover the normal control mechanisms and then discuss the common conditions in which these control mechanisms malfunction. The article will cover calcium and phosphate regulation, vitamin D metabolism and the effects of vitamin D and Parathyroid Hormone. Finally the disordered processes leading to osteomalacia, hyperparathyroidism, renal osteodystrophy, Paget's disease and Osteoporosis will be discussed. Detailed discussion of the clinical manifestations and treatment and of these conditions lies outside the scope of this review but certain aspects will nevertheless be discussed.

Control mechanisms and homeostatic feedback loops

There are a number of complex and interlinked feedback loops that are involved in the control of bone metabolism and calcium levels. These can be broken down conceptually into the feedback loops for control of calcium and phosphate levels, and the feedback loops that control bone formation and bone destruction.

Control mechanisms for calcium levels in the serum

The level of calcium in the serum is largely controlled by two hormones; parathyroid hormone (PTH) and the active form of vitamin D (1,25-Dihydrocholecalciferol or Calcitriol). Calcitonin also has an effect on the serum calcium but is thought to be more important pharmacologically than physiologically.

Vitamin D metabolism: the vitamin D cycle is essential for calcium control and bone metabolism. The term "vitamin D" refers to a group of fat soluble compounds based on a 4-ringed cholesterol backbone. The different forms of vitamin D differ in their precise actions.

The two recognized sources of vitamin D are: synthesis in the skin under the influence of sunlight and secondly, from the diet. Vitamin D synthesized in the skin is usually the major source.

In the skin, 7-dehydrocholesterol is converted to Previtamin D_3 under the influence of sunlight and then re-arranged to vitamin D_3 (Cholecalciferol) by a temperature-dependent process. Melanin reduces the production of vitamin D_3 in the skin.

The dietary source of vitamin D is mainly in the form of Ergocalciferol (vitamin D_2), although vitamin D_3 is also used to fortify food. Vitamin D_2 from the gut is incorporated into micelles and then transported to the liver in chylomicrons. Ingested vitamin D can then be stored in the liver and in adipose tissue.

Vitamin D_3 is bound to vitamin D-binding proteins at a single binding site. Under most circumstances 5% or less of the vitamin D binding sites are occupied and, as a result, the metabolic pathway is only disrupted if a large amount of the vitamin D-binding protein is lost (as can happen in Nephrotic syndrome).

To become active, vitamin D from the gut or skin has to undergo two hydroxylations, the first in the liver and the second in the kidneys. The enzyme 25-hydroxylase is responsible for the first hydroxylation in the liver, following which vitamin D from both sources is transported to the kidneys bound to vitamin D-binding proteins. Vitamin D from the two main sources behaves differently; the vitamin D from the gut, being associated with chylomicrons and lipoproteins is more rapidly hydroxylated but has less affinity for vitamin D-binding protein than that from the skin, so it has a shorter half life.

In the renal tubular cells (probably mainly in the distal tubule in normal patients) the 25-hydroxycholecalciferol is released from the vitamin D binding proteins and a second hydroxylation takes place, either to the active form 1,25-hydroxycholecalciferol (1,25 vitamin D), or to the relatively inactive form 24,25-hydroxycholecalciferol. The enzymes responsible are 1-alpha-hydroxylase and 24-alpha-hydroxylase respectively.

The metabolic pathway of vitamin D is summarized in Figure 1.

1-alpha-hydroxylase may also be found in extra-renal sites, such as the skin, osteoblasts and osteoclasts. It should also be noted that it may also be found in grandulomatous disease such as sarcoid, where it is PTH dependent.

The main circulating form of vitamin D in the body is 25-hydroxycholecalciferol, with a half life of two to three weeks.

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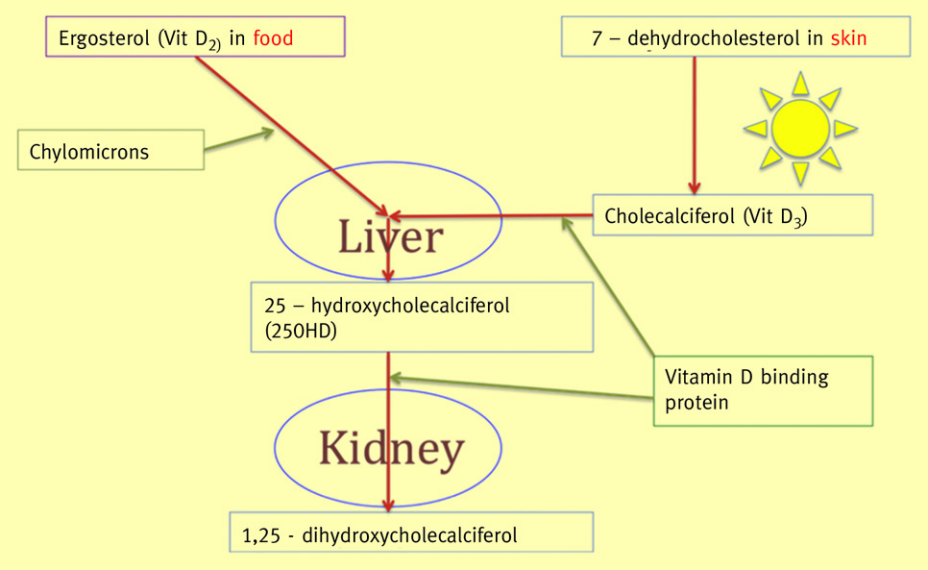

Figure 1 Vitamin D metabolic pathway.

Only about 1% of the vitamin D is usually in the active form, with a half life of 4–6 h.

Production of the active form (1,25 vitamin D) is stimulated by increased levels of PTH (usually in turn in response to decreased calcium levels) or by decreased levels of PO_4.

The actions of active vitamin D: the actions of vitamin D are complex and not yet completely understood. There are at least 25 different metabolites of vitamin D, which have differing actions and functions.

1,25 vitamin D acts directly on the intestine, the kidneys, bone and the parathyroid gland:

Intestine – vitamin D increases the absorption of both calcium and phosphate. It should be noted that high dose glucocorticoids inhibit the vitamin D dependent absorption of calcium from the intestine.

Kidney – vitamin D decreases calcium excretion.

Parathyroid gland – PTH production is suppressed. Vitamin D binds to a single Class II steroid receptor and inhibits PTH gene expression and also inhibits parathyroid cell proliferation.

Bone – regulates osteoblast function and facilitates PTH induced osteoclast activation.

The **net effect** in most cases is to increase both calcium and PO_4 levels in the blood and to aid bone formation, but in high doses, in the presence of calcium and PO_4 deficiency it may cause bone resorption. In other words the net effect of vitamin D varies according to circumstances.

The regulation of active vitamin D: the metabolism of vitamin D into its active or inactive forms in the kidney is regulated by a complex control mechanism that involves other factors, including Fibroblast Growth Factor 23 (FGF23). FGF23 inhibits the formation of 1,25 vitamin D and stimulates the production of 24,25 vitamin D. FGF23 also inhibits the PO_4 reabsorption in the kidney, thus reducing PO_4 levels. *FGF23 degradation is impaired in hereditary hypophosphataemic rickets.*

Under normal circumstances the increased PO_4 loss due to the action of FGF23 is balanced by the increased PO_4 absorption from the intestine under the influence of 1,25 vitamin D.

The process is illustrated in Figure 2.

Parathyroid hormone: parathyroid hormone (PTH) is the primary regulator of serum calcium levels. The hormone is synthesized by the cleavage of pre-pro-PTH, an amino acid polypeptide. This occurs in 2 stages: initially to a 90 amino acid chain compound and then to the active PTH 1-84. If the active form is not required, PTH 1-84 is rapidly degraded to inactive forms. The half life of PTH 1-84 is 2–4 min.

The actions of PTH – PTH mainly acts on the kidney and bone:

Kidney – increases active reabsorption of calcium in the distal nephron

– decreases renal reabsorption of PO_4

Bone – releases calcium from skeletal stores, increases bone resorption

– releases PO_4 from bone

Net effect – increases serum calcium. The renal and bone effects on PO_4 can balance each other.

Just as the effect of vitamin D on bone can vary according to circumstances, the effect of PTH on bone varies according to the length of time for which the PTH acts; if there is a chronic continuous excess then bone is resorbed (mainly via the effect on RANKL and Osteoprotegerin) but intermittent peaks of PTH, occurring in a pulsed fashion, have an anabolic effect on bone.

Response to low serum calcium levels – there is a progressive response to lowered serum calcium levels depending on the duration of depression of the level: PTH is secreted within seconds to minutes of a fall in serum calcium. Within the first hour (often within minutes) active PTH degradation in the parathyroid cells is decreased. Within hours to days there is increased PTH gene expression and after days to weeks parathyroid cells increase in number.