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Preventing and treating deficiency in bone mineralization

Focus on calcium and alphacalcidol combination

INTRODUCTION

Calcium is a major mineral element of the body. It constitutes 1.5-2% of the body weight of an adult human. An average body contains about 1200 g of calcium of which over 98% is found in the bones. The amount of calcium in the blood is usually about 10 mg/dl. Bone mass increases faster than body weight during growth, which necessitates a concomitant increase in body calcium.

Calcium has a number of crucial physiological functions, including formation of bones and teeth, blood coagulation, muscle contraction, neuromuscular transmission, cardiac action, milk production, cellular communication, exocytosis, endocytosis, maintenance of cell membrane and metabolism of enzymes and hormones.

Calcium homeostasis has two principal goals.[1] First, there must be adequate net intake of calcium to permit normal skeletal growth and mineralization. Second, there is tight regulation of the serum calcium concentration in order to permit normal physiologic functioning.

MECHANISM OF CALCIUM BALANCE

There is a dynamic equilibrium between the calcium in the blood and that in the skeleton, which is determined by the exchange of calcium between the skeleton, the intestine and the kidney. This equilibrium is maintained by a complex hormonal system, including interaction of calciotrophic hormones (vitamin D), parathyroid hormone, and probably calcitonin. It is also influenced by sex hormones, growth hormones, corticosteroids and a variety of other locally acting hormones.

Acutely, this system relies on the large reservoir of calcium that is present in bone. Chronically, there must be a balance between calcium intake from the gastrointestinal tract and calcium losses, mostly via the urine.

Maintenance and accretion of body calcium require gastrointestinal absorption, which occurs predominantly in the duodenum and jejunum. Even though there is some passive calcium absorption when dietary intake is high, an active transport system is responsible for most gastrointestinal absorption, especially when dietary intake is low. Overall, about 20-30% of dietary calcium is normally absorbed. Absorption of calcium is enhanced by vitamin D and decreased by the presence of phytates, oxalates and fatty acids in the diet. The kidneys control calcium excretion and parethyroid hormone (PTH) is the principal regulator of urinary calcium excretion. The calcium in the plasma that is not bound to protein, including the ionized calcium and calcium complexed to anions, is freely filtered by the glomerulus and is later reabsorbed by proximal tubule and the loop of Henle under the influence of PTH. 1,25-dihydroxy vitamin D also stimulates calcium reabsorption in the distal nephron.[2]

ROLE OF VITAMIN D

Vitamin D by itself is metabolically inactive unless it undergoes transformation into several metabolites and finally to its active metabolite 1,25-dihydroxy cholecalciferol. The synthesis of this active metabolite involves initial hydroxylation in the liver forming 25-hydroxy vitamin D, followed by second hydroxylation in the kidney with the help of enzyme 1 α-hydroxylase. Modifying the synthesis of 1,25-dihydroxy vitamin D is an important mechanism for regulation of calcium balance (Figure 1).[1,2]

The activity of 1,25-dihydroxy vitamin D on the intestinal tract

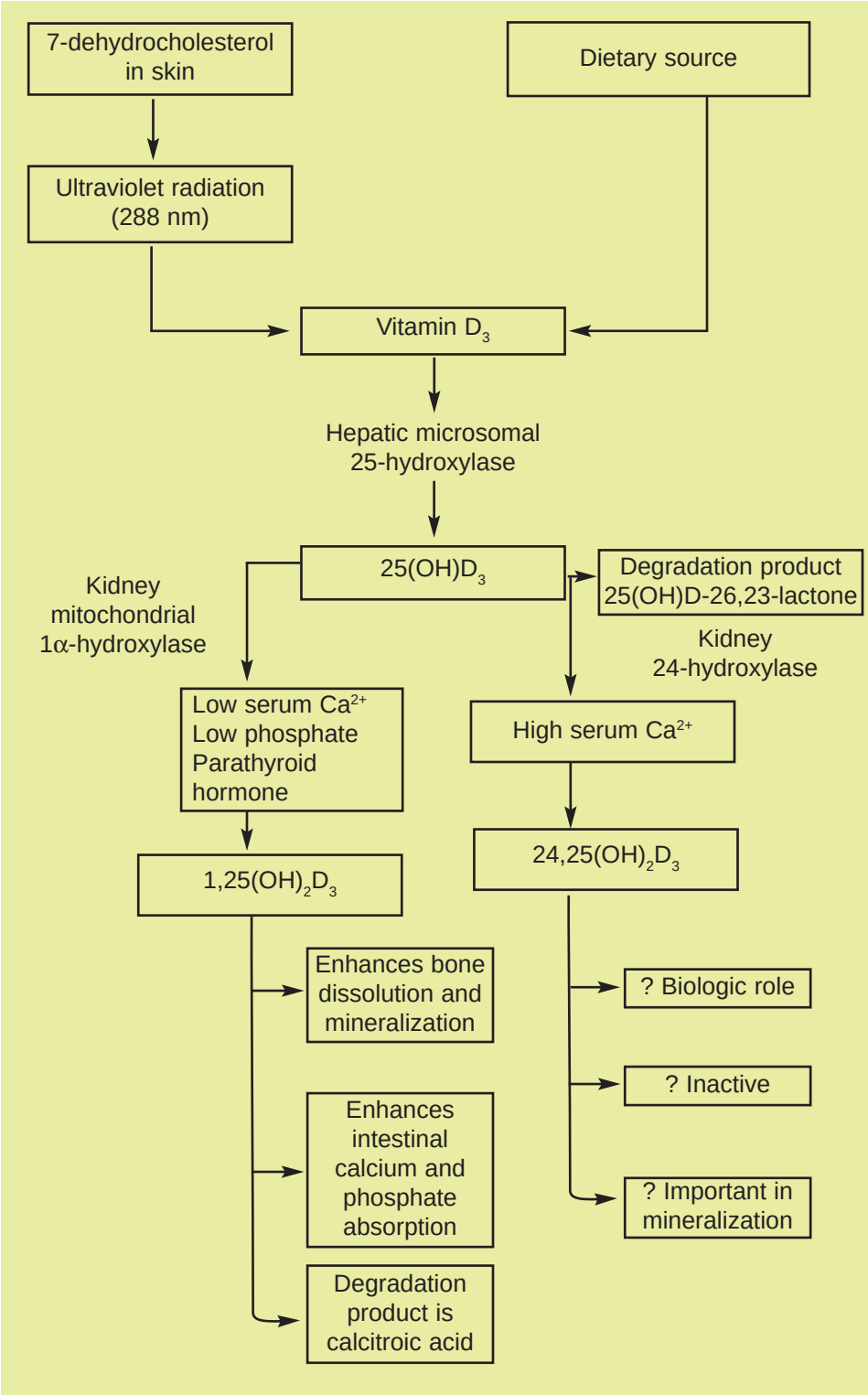

Figure 1.The metabolic pathway of vitamin D, indicating its conversion to the hormone 1,25 $(OH)_2D_3$ and to 24,25 $(OH)_2D_3$.

controls calcium intake. Through the production of calcium-binding proteins and activation of a calcium pump on the gastrointestinal epithelial cells, 1,25-dihydroxy vitamin D stimulates the active transport of calcium. Without adequate 1,25-dihydroxy vitamin D, the active form of vitamin D, gastrointestinal absorption of calcium decreases substantially.

Lack of vitamin D may lead to a condition called rickets, especially in children, in which bones and teeth become weak. In adults, it may cause a condition called osteomalacia, in which calcium is lost from bones so that they become weak.

Vitamin D is also sometimes used to treat other diseases in which calcium is not used properly by the body.

VITAMIN D ANALOGUES

Primary deficiency of vitamin D, caused by low dietary vitamin D, intestinal malabsorption or reduced exposure to sunlight, can be corrected with native vitamin D supplements. These supplements are safe, cheap and readily available without prescription.

Reduced renal activation, which may occur in the elderly, can cause secondary vitamin D deficiency. Native vitamin D cannot correct this type of deficiency but vitamin D analogues prove effective. Alphacalcidol requires activation by the liver, which can occur even with serious liver disease. Calcitriol needs no activation but may induce hypercalcemia when taken due to its unregulated concentrations. Hypercalcemia is less likely to occur with alphacalcidol as conversion to calcitriol is relatively slow, producing lower peak concentrations.

Vitamin D analogues appear to outshine native vitamin D supplements for preventive treatment of osteoporosis. Vitamin D analogues do not accumulate in tissue and can be used in all age groups and types of osteoporosis.[3]

SAFETY AND SUPERIORITY OF ALPHACALCIDOL

Alphacalcidol, chemically known as l α-hydroxy vitamin D_3 is fat soluble and up to 100% absorption normally takes place. After absorption, alphacalcidol is rapidly hydroxytated at position 2, predominantly in liver although the enzyme is widely distributed in body tissues. Alphacalcidol undergoes rapid hepatic conversion to 1,25-dihydroxy vitamin D_3, which acts as a regulator of calcium and phosphate metabolism. Due to this rapid conversion, the therapeutic benefits of alphacalcidol are virtually the

same as those of 1,25-dihydroxyvitamin D_3. The main effects are to increase circulating 1,25-dihydroxy vitamin D_3 levels, and thereby to increase intestinal absorption of calcium and phosphate, promote bone mineralisation, regulate plasma PTH levels as well as to decrease bone resorption, with relief from bone and muscle pain.[4]

A review of more than 20 clinical reports indicates that l α–hydroxy D_3 is rarely associated with hypercalcemia or hyperphosphatemia, or impairment in renal function.

Alphacalcidol has a clinical edge over calcitriol; there is evidence that calcitriol impairs creatinine secretion by renal tubule due to which serum creatinine levels may increase and measurements of creatinine clearance may fall during calcitriol therapy in patients with mild-to-moderate renal failure.[5]

CLINICAL EFFICACY

Effects of alpha-calcidiol (1 alpha-hydroxy-cholecalciferol) were evaluated on the serum levels of osteocalcin in involutional osteoporosis. 1 alpha-hydroxycolecalciferol 1.5 micrograms was administered for 5 days and the effects were measured on serum osteocalcin (OC) and other parameters of bone and mineral metabolism in 20 osteoporotic women and 11 age-matched normal women. A statistically significant ($p<0.01$) increase of serum OC, calcium and phosphate and urinary calcium and hydroxyproline was observed. In contrast, alkaline phosphatase was unchanged. This study concluded that the increase of serum OC with alphacalcidiol was comparable to the control group and by means of an index that reflects the global activity of the skeleton. No apparent defect of osteoblastic responsiveness to the drug in osteoporotic subjects was found.[6]

Dukas and colleagues performed a community-based, randomized, double-blind, placebo-controlled trial to investigate whether supplementation with alphacalcidol reduces falls in community-dwelling elderly men and women.[7] This study found that the supplementation with alphacalcidol for 36 weeks reduced the number of fallers and falls in an elderly community-based population when the minimum daily calcium intake was 512 mg or more. It also increased serum calcium levels and decreases PTH secretion. The study suggests that there is a synergistic effect of vitamin D and calcium on muscle weakness and bone fragility.

CALCIUM SUPPLEMENTS

Physiological changes in calcium balance occur during growth, pregnancy, and lactation and with increasing years. In children, a net positive calcium balance is necessary for growth and skeletal mineralization. Calcium absorption, to some extent, is regulated by the physiological requirements and demands of the body. Elderly persons have reduced exposure to sunlight and dietary vitamin D intake, and even persons with normal serum vitamin D levels may have 1,25-dihydroxy vitamin D_3 deficiency because of a variety of metabolic factors. In such patients, daily calcium intake along with alphacalcidol has a positive effect on bone metabolism and muscle strength.

RATIONALE OF COMBINATION

Alphacalcidol increases the intestinal absorption of calcium. If calcium is readily available in the same preparation, better and proper absorption of calcium will occur. Calcium supplementation along with alphacalcidol has shown to have a beneficial effect in osteoporosis. Calcium supplementation is usually done with 0.5-2 g per day of calcium carbonate, gluconate, lactate, etc. Calcium carbonate is converted to calcium chloride by hydrochloric acid in stomach where 39% of it is absorbed. It is absorbed as free calcium and bicarbonate ions and is not metabolised. The calcium content of calcium carbonate is 40% and 500 mg calcium carbonate contains 200 mg elemental calcium, which is the least recommended dose of calcium. Moreover, the dosage of alphacalcidol required is also reduced to some extent. So, this combination is economic and beneficial for the patient.[4]

CONCLUSION

Calcium and vitamin D are the two most important determinants of calcium balance and bone mineralization. Vitamin D analogues have emerged as a promising option to enhance calcium absorption from the dietary intake. Alphacalcidol, which is converted into the active metabolite in liver, increases calcium absorption and osteoblastic activity and reduces urinary calcium loss and osteoclastic activity. It is safe and well-tolerated in most patients including those with chronic renal failure. Combined with oral calcium, it improves bone mineralization and minimizes the risk of hypercalcemia.

A combination of calcium with alphacalcidol is indicated in osteoporosis, renal bone disease (renal osteodystrophy), hypoparathyroidism, hyperparathyroidism (with bone disease), rickets and osteomalacia and chronic renal failure and conditions associated with gastric hyperacidity.

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