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 parathyroid 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 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
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 1α-hydroxy vitamin D₃, is fat soluble and up to 100% absorption normally takes place. After absorption, alphacalcidol is rapidly hydroxylated 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 D₃, 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 D₃. The main
effects are to increase circulating 1,25-
dihydroxy vitamin D₃ 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 1α−hydroxy-
D₃ 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-
hydroxycholecalciferol) were
evaluated on the serum levels of
osteocalcin in involutional
osteoporosis. 1 alpha-
hydroxycholecalciferol 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 alphacalcidol 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 D₃ 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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