Factors Affecting Calcium Metabolism in Disorders of the Kidney*

MURRAY J. FAVUS, M.D.

Department of Medicine, Michael Reese Hospital and Medical Center, and the University of Chicago Pritzker School of Medicine, Chicago, IL 60616

ABSTRACT

The ionized calcium concentration in blood is maintained within narrow limits by a complex hormonal system that includes parathyroid hormone (PTH) and vitamin D. The kidney plays a pivotal role in the physiologic action of PTH, as this peptide hormone increases tubular calcium reabsorption, decreases tubular phosphate reabsorption, and stimulates the renal 25-hydroxy-1-hydroxylase to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, the hormonal form of the vitamin that stimulates intestinal calcium absorption. Inherited and acquired disorders of tubular function and acute and chronic renal failure may disturb normal renal handling of calcium and phosphorus and the hydroxylation of 25-hydroxyvitamin D. As a result, decreased intestinal calcium absorption and hypocalcemia cause parathyroid hyperplasia and metabolic bone disease.

Introduction

A complex hormonal system regulates the distribution and concentration of calcium in the body. A variety of bodily functions depends upon the critical level of ionized calcium in blood including muscle contractility, nerve conduction, coagulation activation, hormone secretion, and enzymatic activity. However, extracellular calcium represents only one percent of total body calcium; the remaining 99 percent exists as part of the hydroxyl-apatite crystal structure of bone. The daily influx of absorbed dietary calcium could cause fluctuations in blood calcium concentration. As such perturbations would disturb calcium-dependent processes, the vitamin D-parathyroid hormone system must control the thruflux of calcium and phosphorus to bone and at the same time maintain blood ionized calcium concentration within narrow limits. The kidney plays an important role in both the quantitative conservation of calcium and the maintenance of serum calcium. This paper reviews the normal physiology of calcium metabolism with emphasis on the role of the kidney and reports the changes in calcium metabolism caused by renal glomerular and tubular dysfunction.

* Supported by grant AM 20585, National Institutes of Health, Bethesda, MD 20014.
Normal Calcium Physiology

Calcium Balance

The average adult in North America ingests 800 to 1000 mg of calcium daily of which only a fraction, 30 to 45 percent, is absorbed. The remainder, along with 150 to 200 mg secreted into the bowel, comprises the fecal calcium content. In adults, some 300 mg of calcium is resorbed from bone per 24 hours and a lesser amount is incorporated into bone. The difference between resorption and accretion accounts for the gradual loss of bone mass that begins in the third and fourth decade of life.15 Urinary calcium excretion represents a major route of calcium loss; excretion rates greater than 250 mg for women, 300 mg for men or 4 mg per kg either sex, is considered excessive.4 Net intestinal absorption (dietary ingested-fecal) must match urinary calcium excretion to maintain calcium balance.

Intestinal Calcium Absorption

Dietary calcium is absorbed by both small and large intestine. Passive diffusion and active transport mechanisms account for the movement of calcium across the intestinal mucosa to the capillary beds. The active transport mechanism is vitamin D-dependent and is subject to regulation, depending on body calcium requirements.12 During growth, pregnancy, lactation or when the diet is low in calcium, the efficiency of dietary absorption increases by increasing calcium active transport.12 The process resides primarily in duodenum, ileum, and colon and is stimulated by the hormonal form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)₂D].

Vitamin D Metabolism

Vitamin D₃ (cholecalciferol) is synthesized in the skin by a non-enzymatic reaction driven by ultraviolet irradiation of natural sunlight. Dietary sources of vitamin D₃ include fortified foods and multivitamin tablets. Synthetic vitamin D₂ (ergocalciferol) is also added to foods and vitamin pills. Therefore, vitamin D₂ and D₃ compose the vitamin D stores of the body. Both are largely metabolized in the liver to 25-hydroxyvitamin D (25OHD), which returns to the circulation and represents the major form of vitamin D in blood.18 The kidney is the site of the hydroxylation of 25OHD. The 1-hydroxylation of 25OHD takes place in the mitochondria of proximal renal tubules.13 The product, 1α,25(OH)₂D, is the most potent form of vitamin D in stimulating intestinal calcium absorption and bone resorption. In addition, 1,25(OH)₂D also heals rickets and reverses the myopathy of vitamin D deficiency. Blood levels of 1,25(OH)₂D are increased under conditions of increased body calcium needs,10 and the intestinal mucosal content of 1,25(OH)₂D increases, thus stimulating calcium active transport. Parathyroid hormone and low phosphorus stimulate the renal 1-hydroxylase and, by increasing the production of 1,25(OH)₂D, play a role in the adaptation to body calcium requirements.10

Other renal metabolites of 25OHD include 24,25(OH)₂D, 25,26(OH)₂D, and 1,24,25(OH)₃D.5 The physiologic roles of these metabolites are unknown, but some evidence suggests that either 25OHD or 24,25(OH)₂D may be required for bone mineralization in addition to 1,25(OH)₂D.

Serum Calcium

Forty-five to 48 percent of blood calcium exists in the ionized state and 42 to 45 percent is protein-bound, largely to albumin; a small fraction circulates as soluble complexes. Ionized and complexed calcium are filtered at the glomerulus, but only one to five percent appear in the final
Parathyroid Hormone

The maintenance of ionized calcium in blood is dependent upon the actions of PTH. The parathyroid glands secrete PTH in response to a fall in the ionized calcium concentration; low magnesium also stimulates PTH secretion, but is less potent than calcium. Increased serum phosphorus may depress serum calcium and so, secondarily, increases PTH. Parathyroid hormone is synthesized and stored as a larger molecule, 90 amino acids, called proPTH. The six amino terminal amino acid chain is cleaved prior to secretion, so the 84 amino acid PTH molecule is the major form of the hormone secreted. The major actions of PTH involve kidney and bone. All of the actions of PTH serve to maintain the serum ionized calcium concentration. PTH stimulates bone resorption, causing degradation of the hydroxyapatite crystal and the release of calcium and phosphate into the extracellular space.

Parathyroid hormone has three major actions on the kidney. The hormone stimulates distal tubular reabsorption of calcium. This efficient reabsorption mechanism is a critical feature of the renal actions of PTH in controlling blood ionized calcium. Also, PTH reduces proximal reabsorption of phosphate, causing an increase in urinary phosphate excretion. This action serves to reduce blood inorganic phosphate concentration and prevents a potential rise in blood phosphate caused by phosphate release from bone. Thirdly, PTH increases the conversion of 25OHD to 1,25(OH)₂D by stimulating renal tubular 1-hydroxylase activity. As a result, intestinal calcium absorption increases. All of the actions of PTH appear to be mediated by the intracellular generation of 3',5'-cyclic adenosine monophosphate (AMP). Urinary concentrations of cyclic AMP increase during PTH stimulation, and such measurements have been used to assess parathyroid secretion rates.

Disorders of Renal Tubule Function

Phosphate Transport

Defective tubular reabsorption of phosphate causes phosphaturia and hypophosphatemia. Low phosphate disrupts normal mineralization and causes a bone disease indistinguishable from that of vitamin D deficiency, rickets in children and osteomalacia in adults. Genetic disorders of tubular phosphate transport appear as isolated defects, as in X-linked hypophosphatemic rickets, also known as vitamin D-resistant rickets. A similar inherited defect in phosphate transport may also occur in conjunction with disorders of the renal tubular transport of uric acid, glucose, and amino acids. Known as the Fanconi Syndrome, the disorder may also be complicated by rickets. Certain rare mesodermal tumors cause a syndrome of hypophosphatemic rickets, presumably because the tumor produces a phosphaturic substance. In addition, there may be an accompanying defect in 1,25(OH)₂D production, as blood 1,25(OH)₂D are low. Removal of the tumor reverses all of the metabolic changes.

Hydrogen Ion Transport

Hereditary distal renal tubular acidosis is a disorder of hydrogen ion transport that causes hydrogen ion retention, metabolic acidosis, and defective mineralization. The acidosis also causes hypercalciuria and mild secondary hyperparathyroidism. Depressed bone mineralization is perhaps due to the acidosis and reduced 1,25(OH)₂D production. Suffi-
cient alkali administration corrects the acidosis and permits the rickets to heal. Other inherited renal tubular defects causing metabolic acidosis and the several acquired metabolic acidoses are not associated with metabolic bone disease.

**1-Hydroxylase Deficiency**

An absence of the 1-hydroxylase is a rare cause of infantile rickets. The disorder, called vitamin D-dependent rickets, follows an autosomal recessive pattern of inheritance. The enzyme deletion is assumed to be present since blood 1,25(OH)₂D concentrations are low and small replacement doses of 1,25(OH)₂D₃ rapidly and completely correct the hypocalcemia, secondary hyperparathyroidism, and ricketic bone disease. Vitamin D-dependent rickets can be differentiated from vitamin D-resistant rickets by the early onset of severe hypocalcemia and rickets and the efficacy of 1,25(OH)₂D₃ in the former and the large doses of oral phosphate required in the latter.

**Parathyroid Hormone Resistance**

Inherited target organ resistance to endogenously secreted PTH results in hypocalcemia and hyperphosphatemia. This entity, pseudohypoparathyroidism, can be distinguished from conditions in which there is a genetic absence (idiopathic hypoparathyroidism) or surgical absence (postsurgical hypoparathyroidism) of the parathyroid glands by the high blood levels of immunoreactive PTH and lack of response to exogenous PTH. The disorder tends to be familial and is accompanied by somatic changes including short stature, round facies, mental retardation, and skeletal abnormalities such as short metacarpals. Resistance to PTH may affect all of the actions of PTH on kidney and bone or some PTH actions may be present along with selective unresponsiveness, creating several rare syndromes. Defective or absent receptor-cyclase coupling protein, a component of the adenylate cyclase located in the cell membrane of PTH-responsive cells, may be responsible for the PTH resistance.

**Glomerular Disease**

**CHRONIC RENAL FAILURE**

Reduction in functioning renal mass is the central cause of the deranged calcium metabolism and the development of metabolic bone disease in chronic renal failure. Hypocalcemia results from two processes related to decreased renal tubular function. First, insufficient 1,25(OH)₂D production decreases intestinal calcium absorption. Secondly, phosphate excretion is impaired as the number of functioning nephrons is reduced, and phosphate retention and a rise in serum phosphate occur when glomerular filtration rate falls below 25 ml per min. Hyperphosphatemia reduces serum calcium. Initially, hypocalcemia may be corrected by increased PTH secretion, but prolonged hypocalcemia causes increased PTH secretion, secondary hyperparathyroidism, and a considerable increase in the size of the glands. Chronic parathyroid hyperplasia causes overproduction and loss of regulation of PTH. As a result, PTH-stimulated osteoclastic bone resorption eventually causes bone loss sufficient to produce pain, deformity, and fracture.

Chronic hemodialysis reverses many of the manifestations of uremia, but metabolic bone disease may progress and become disabling. Secondary hyperparathyroidism can be reversed by correcting the hypocalcemia. This can be done by 1,25(OH)₂D₃ administration and adding calcium to the dialysate. However, chronic parathyroid hyperplasia may continue despite normalization of serum calcium, requiring total parathyroidectomy. Hyperparathyroidism must be controlled prior to renal transplantation, lest the transplanted kidney be damaged by
hypocalcemia and calcium phosphate deposition in the renal parenchyma.

Iliac crest bone biopsy provides the opportunity to establish a histologic diagnosis of the skeletal process. Commonly, components of both bone resorption, osteitis fibrosa, and defective mineralization, osteomalacia, are present. Blood chemistries and radiologic evaluation are helpful but not diagnostic. Elevation of bone alkaline phosphatase indicates increased osteoblastic cell activity, but it may be associated with both osteitis fibrosa and osteomalacia. Skeletal roentgenograms may show signs of bone resorption or defective mineralization, but extensive histologic changes may be present before the radiographs become abnormal.

It is noted that 1,25(OH)2D3 usually heals osteomalacia, but some patients may require other metabolites such as 250HD and 24,25(OH)2D. A consequence of chronic dialysis is aluminum retention. Toxic levels may be reached in the brain and bone in some patients, with the primary manifestations being central nervous system deterioration and defective mineralization. The accompanying bone defect has the histologic appearance of vitamin D deficiency osteomalacia, but it is not reversed by 1,25(OH)2D3 administration.

ACUTE RENAL FAILURE

The course of acute tubular necrosis may be complicated by phosphate retention, hypocalcemia, and increased PTH. As glomerular and tubule function are restored, phosphate diuresis reduces serum phosphate, and the metabolic abnormalities are reversed.

NEPHROTIC SYNDROME

Patients with nephrotic syndrome have low serum 250HD levels, presumably owing to the urinary loss of the vitamin D-binding protein and the 250HD bound to it. The low serum 250HD may be se-

vere and cause osteomalacia which is corrected by large doses of vitamin D.14 No measurements of 1,25(OH)2D are available, but they are presumed to be low because of low 250HD substrate.

References


12. KIMBERG, D. V., SCHACHTER, D., and SCHENKER, H.: Active transport of calcium by


