Divalent Ion Regulation and Disorders

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Calcium

Calcium Homeostasis

Calcium, the most abundant cation in the body, represents about 2% of the total body weight. More than 99% is in bone, and is unavailable for participation in the immediate regulation of calcium homeostasis, while the remainder is distributed in the teeth, soft tissues, and the extracellular space. A 70-kg man has approximately 1.2 kg of calcium, of which only 1.3 g is extracellular. In the normal human adult, neutral calcium balance is maintained over a wide range of intakes, 500 – 1500 mg/day. In plasma, normal calcium concentrations vary from 8.8 – 10.4 mg/dL and is composed of 3 fractions. Approximately 40% of the total serum calcium is protein bound (non-ultrafiltrable). Seventy-five to 90% of this fraction is bound to albumin, and the remainder to globulin. An additional fraction (10 %) of total serum calcium is complexed to various anions, including phosphate, bicarbonate, and citrate, but is ultrafiltrable. The remainder is free ionized calcium (50%). The ionized calcium is the physiologically important component, available for transport and cellular metabolism, and can easily be measured directly. In the absence of measurements of ionized calcium, one can attempt to correct the total calcium for changes in serum protein concentration and changes in blood pH. Thus, an approximation may be obtained as follows: for every gram/dL that serum albumin differs from 4 g/dL, the serum calcium should be adjusted by 0.8 mg/dL. Similarly, for every 0.1 increment in pH, serum calcium should be decreased by 0.12 mg/dL. Generally, as blood pH decreases, the ultrafiltrable and ionized fractions increase. This increase is due not only to a decrease in the affinity of albumin for calcium but also to a decrease in calcium complexed with plasma anions, especially phosphate and bicarbonate. However, when total plasma calcium is normal, the change in the ultrafiltrable and ionized fractions with blood pH is generally insignificant except in severe acidosis (pH < 7.30) or severe alkalosis (pH > 7.60) [1]. Total cell calcium concentration ranges from 1 to 5 mM; however, most of this is bound to the external cell membrane surface, resulting in an intracellular calcium of about 0.5 mM. Most of this is either sequestered in the endoplasmic reticulum and mitochondria or bound to cytoplasmic proteins and ionic ligands, resulting in an intracellular calcium concentration of about 100 nM [1]. The precise regulation of intracellular calcium is important for its role in regulating many biological processes.

Calcium Metabolism

Normal plasma calcium concentration is maintained by the close regulation of intesti-

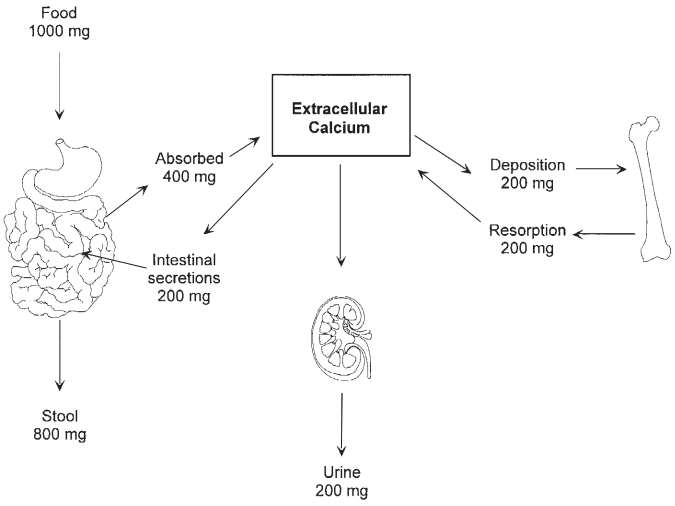

Figure 1. Scheme for calcium balance.

nal calcium absorption, renal calcium reabsorption, and retention and release of skeletal calcium. These 3 biological processes are regulated by the combined effects of parathyroid hormone (PTH) and vitamin D. The overall scheme for calcium balance is depicted in Figure 1. On a usual daily intake of approximately 1000 mg, a net absorption of 200 mg will occur. About 200 mg will enter and leave the bone, and approximately 200 mg will be excreted by the kidney to maintain balance. During growth, the need for positive calcium balance is substantial, and up to 400 mg of calcium/day can be deposited in the growing human skeleton. The level of ionized calcium in blood is tightly controlled despite a wide range of calcium influx from the intestine and bone. This tight control depends in a major way on the parathyroid glands that monitor plasma calcium and increase secretion of parathyroid hormone (PTH) in response to decreases in ionized calcium (Figure 2). This increase in PTH stimulates bone resorption resulting in the release of calcium and phosphorus. PTH acts upon the kidney to increase the reabsorption of calcium and stimulates production of calcitriol, which then increases intestinal calcium and phosphorus absorption. The increased influx of phosphorus from the intestine and bone is excreted by the actions of PTH upon the kidney, thereby restoring homeostasis.

The nature of the calcium sensing by the parathyroid gland has been recently elucidated following the cloning of a G protein-coupled, calcium-sensing receptor from bovine [2] and human [3] parathyroid glands, and rat [4] and human kidney [5]. The deduced amino acid sequence of this receptor shows the characteristic 7-membrane-spanning signature found in all G protein-coupled receptors, and it has some amino acid similarity to the metabotropic glutamate receptors in the central nervous system (CNS). A variety of cells can directly recognize and respond to small changes in their ambient calcium level through this receptor, and it may mediate several of the known effects of calcium on parathyroid and renal function. The physiological relevance of this receptor in calcium homeostasis in man has been demonstrated by the identification both of inactivating and activat-

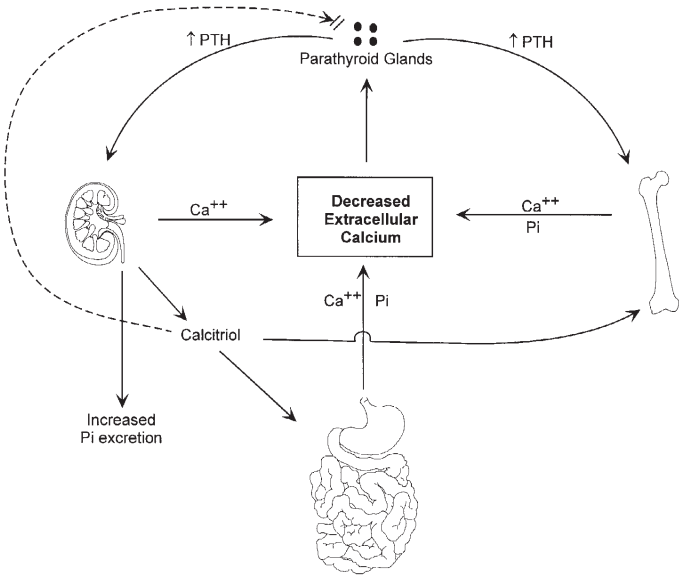

Figure 2. Parathyroid gland response to decreases in ionized calcium.

ing mutations in this calcium-sensing receptor, which result in hypercalcemic (familial hypocalciuric hypercalcemia) and hypocalcemic (neonatal severe hypocalcemia and autosomal dominant hypocalcemia) phenotypes, respectively [6, 7].

Intestinal Calcium Absorption

Net intestinal absorption averages 25 – 30% of a normal dietary intake [1]. The efficiency of intestinal absorption increases as dietary calcium is reduced, so that neutral calcium balance can be maintained at intakes as low as 150 mg/day. The efficiency of absorption normally increases during periods of increased skeletal mineralization, such as growth and pregnancy, and with administration of vitamin D metabolites. Intestinal absorption declines with age, during vitamin D depletion, and during increased intake of oxalate and phytic acid (abundant in many plant tissues).

Regulation of Calcium Absorption

Absorption of calcium across the intestinal mucosa is achieved by 2 processes that occur in tandem: an active transcellular transport (saturable and energy-requiring) and a passive paracellular diffusion process (nonsaturable) [1]. The duodenum is the major site of the active transport process, while the passive mechanism occurs throughout the small intestine and the colon. The absorption rate in all intestinal segments is increased by vitamin D, with the duodenum being the most responsive.

The active mechanism involves transport across the apical membrane, transport across the cytosol, and extrusion across the basolateral membrane. The initial entry involves calcium channels. Within the cell, calcium is bound to a calcium-binding protein, calbindin, which probably protects against toxic increases in cytosolic calcium and transports the calcium across the cell to the basolateral membrane. An ATP-dependent calcium pump in the basolateral membrane that has a higher

affinity for calcium than calbindin is responsible for the extrusion of calcium from the cell. The regulation of calbindin and the plasma membrane calcium pump is vitamin D dependent [8]. This active component becomes saturated at relatively low calcium intake (< 500 mg/day). When daily calcium intake exceeds 500 mg, passive paracellular absorption occurs, which depends on and varies linearly with intestinal calcium concentration and is driven by electrical and chemical gradients. It is nonsaturable; however, there is a possibility that tight junction mediated calcium transport may also be regulated by calcitriol.

The major regulator of intestinal calcium absorption is calcitriol which acts through genomic and nongenomic mechanisms. The genomic mechanism is analogous to that of other steroid hormones in that the ligand, calcitriol, binds to the vitamin D receptor (VDR). Calcitriol regulates the transcription of many genes including that for VDR, calbindin, and the plasma membrane calcium pump. Following administration of calcitriol, there are increases in VDR, calbindin and calcium pump, which correspond to an increase in calcium transport. In addition, there is strong evidence for a rapid nongenomic effect of calcitriol on calcium absorption (transcaltachia) that is independent of the requirement for gene transcription. This effect occurs very rapidly, within seconds to minutes, and is too rapid to be the result of gene transcription [9].

While vitamin D is the most important systemic factor involved in the regulation of calcium absorption, a variety of other factors may also play a role. Many of these factors, such as PTH, growth hormone, estrogen, and loop diuretics, increase intestinal absorption indirectly by increasing the synthesis of calcitriol. On the other hand, glucocorticoids, metabolic acidosis, and thiazide diuretics may decrease intestinal calcium absorption. Other substances within the intestinal lumen, such as phosphate, oxalate, long chain fatty acids, and fiber, decrease calcium absorption. Conversely, lysine, arginine, and lactose increase calcium absorption [10].

Renal Handling of Calcium

To maintain balance, the kidney needs to excrete an amount of calcium which is equal to the daily net intestinal calcium absorption (approximately 200 mg). Renal excretion of calcium begins with the filtration of the ultrafiltrable fraction of plasma calcium (UFCa). This and the glomerular filtration rate (GFR × UFCa) comprise the filtered load of approximately 9,000 mg/day. Therefore, 98 – 99% (8,800 mg/day) needs to be reabsorbed to allow the excretion of 200 mg/day, which is required to maintain balance. Approximately 70% of filtered calcium is reabsorbed in the proximal convoluted tubule (PCT), 20% in the thick ascending limb of the loop of Henle, 5 – 10% in the distal tubule, and < 4% in the collecting tubule. Transcellular transport across the renal tubular cell resembles that which occurs in enterocytes [1]. As in the intestine, a large proportion of the transport occurs via the paracellular pathway.

In the PCT, reabsorption of calcium is largely passive and is proportional to sodium and water reabsorption [11]. Reabsorption is enhanced by extracellular fluid (ECF) volume contraction and is diminished by ECF volume expansion. In the proximal straight tubule, calcium is transported against both electrical and chemical gradients, suggesting that the transport process is energy-requiring, active, and dissociable from sodium and water transport [12]. Most studies show that reabsorption of calcium in the medullary portion of the thick ascending loop of Henle is passive,

driven by the positive luminal potential, which depends on the activity of the Na-K-2Cl transporter. Hormonal regulation may also occur in this segment.

In the distal convoluted tubule (DCT), only 5 – 10% of calcium reabsorption occurs. The transport process is active, occurring against an electrochemical gradient, and it can be dissociated from sodium reabsorption by administering a thiazide. PTH also enhances calcium reabsorption independent of changes in sodium reabsorption or luminal potential, possibly by stimulating adenylate cyclase in the granular cells [13]. Less than 4% of calcium reabsorption occurs in the collecting duct. Current evidence suggests that the reabsorption process is active, occurring in the granular cortical collecting tubule and is independent of electrical potential or sodium transport [13]. This part of the nephron may play a role in the final regulation of renal calcium reabsorption.

Regulation of Calcium Excretion by the Kidney

Much of the regulation of calcium excretion occurs in the distal tubule where the effects of calciotropic hormones on calcium transport are localized. In general, the process appears to be similar to calcium transport in the enterocyte. A variety of factors may influence the renal handling of calcium [1].

A high intake of dietary calcium will increase urinary calcium excretion, both by increasing the filtered load, if serum calcium increases, and by suppressing PTH. Conversely, phosphate administration tends to decrease urinary calcium excretion by decreasing the filtered load of calcium and by stimulating PTH secretion.

PTH is thought to be the primary homeostatic regulator of renal calcium excretion and serves to increase calcium reabsorption by the kidney; however, increases in serum calcium as a result of the actions of PTH on bone may override this effect so that frank hypercalciuria may occur. Also, PTH has been shown to reduce GFR by altering the K_f of the glomerular capillaries [1]. This reduction in the filtered load of calcium, along with the enhancement of tubule reabsorption, results in decreased calcium excretion. The effects of calcitriol on renal calcium excretion remain ill-defined. It is likely, however, that the direct effect of calcitriol is to increase urinary calcium excretion independent of the changes in PTH and serum calcium.

In general, acidosis is associated with increases in urinary calcium by increasing the release of calcium from bone and by inhibiting tubular calcium reabsorption. Acidosis also increases the proportion of ultrafiltrable calcium by decreasing calcium binding to serum proteins. Alkalosis, on the other hand, tends to reduce urinary calcium by increasing calcium binding to proteins, therefore decreasing free calcium levels and increasing PTH secretion. It has also been shown that alkalosis enhances renal tubular calcium reabsorption independent of any change in PTH. Hypercalcemia of any cause leads to hypercalciuria, especially if PTH secretion is suppressed. Loop diuretics increase calcium excretion by decreasing calcium reabsorption in the loop of Henle. Thiazide diuretics, on the other hand, decrease calcium excretion. Glucose infusion enhances calcium excretion by decreasing calcium reabsorption in the proximal tubule. Insulin infusion and hyperinsulinemia are also associated with hypercalciuria.

Abnormalities in the recently described calcium receptor may also be associated with alterations in calcium excretion such as those found in patients with familial hypocalciuric hypercalcemia [6].

Calcium Metabolism in Bone

Under normal circumstances, there is constant mobilization of calcium from bone and deposition of calcium in newly-formed osteoid as part of the continuous process of normal bone remodeling that occurs throughout life. During growth, the net effect is to deposit calcium into the growing skeleton. The converse, an excessive rate of bone resorption, can be the result of disease states in which the normal coupling between bone formation and resorption is disturbed, leading to net skeletal loss. These diseases include hyperparathyroidism, hypercalcemia of malignancy, multiple myeloma, and osteoporosis.

Several hormones are known to regulate osteocyte and osteoclast activity in bone. PTH is the major regulator of bone turnover. The target cell for PTH is the osteoblast, and effects upon osteoclasts are thought to be indirect. Although PTH stimulates both bone formation and bone resorption, the net effect of sustained increases in PTH is loss of bone. Current evidence indicates that intermittent elevations of PTH may actually be associated with a net increase in bone formation. PTH also increases the conversion of mononuclear cells to osteoclasts. Like PTH, the principal target cell for calcitriol action is the osteoblast. While calcitriol appears to be essential for normal bone growth and mineralization, its net effect on bone formation depends on the balance between the negative effect on osteoblast number and its positive effect on bone formation per osteoblast. The actions of calcitriol are complex and likely related to multiple effects on bone cells, such as enhancing mineralization of osteoid and synthesis of subcellular organelles in osteoblasts and osteocytes, as well as altering the concentration of extracellular calcium and phosphorus. Calcitriol also exerts a permissive effect on PTH-stimulated osteoclastic resorption. Bone remodeling is regulated not only by PTH and calcitriol but also by other hormones such as insulin, growth hormone, calcitonin, IGF-1, glucocorticoids, sex hormones, thyroid hormones, and a variety of locally produced cytokines. Calcitonin inhibits bone resorption and induces hypocalcemia; however, its importance in the daily physiological regulation of skeletal calcium is not known. In addition, bone resorption may be altered by hormone-independent mechanisms such as systemic acidosis, in which bone mineral is released from the skeleton to buffer hydrogen ions.

Hypocalcemia

The hormonal systems responsible for the maintenance of normal plasma calcium concentrations are made up of PTH, vitamin D, and the target organs for these hormones, i.e. bone, kidney, and intestine. Because the presence of both PTH and vitamin D is required for full expression or activity of the other, hypocalcemia may commonly result from a defect in either the PTH or vitamin D system.

The causes of hypocalcemia can be classified into the following categories (Table 1):

Decreased PTH secretion may be due to idiopathic or acquired hypoparathyroidism [14]. Idiopathic hypoparathyroidism, which is relatively rare, may be familial or sporadic and can present at any age. Surgical hypoparathyroidism may result from thyroid, parathyroid, or radical neck surgery and may be transient or permanent [15]. Hypoparathyroidism has been reported with parathyroid infiltration by malignancy, iron, copper, and possibly amyloid [16 – 19], and also following neck irradiation. Hypomagnesemia causes hypocalcemia by decreasing the release of PTH and may impair PTH-induced

Table 1. Causes of Hypocalcemia

Disorders of the parathyroid
- Decreased PTH secretion
  - – Hypoparathyroidism
  - – Idiopathic, surgical, infiltrative, radiation-induced, magnesium depletion
- PTH resistance
  - – Pseudohypoparathyroidism Type 1a, 1b, 1c, 2
  - – Magnesium depletion
  - – Renal failure

Disorders of vitamin D metabolism
- Vitamin D deficiency
  - – Dietary
  - – Malabsorption
  - – Lack of exposure to sun
- Decreased production of 25(OH)D_3
  - – Severe liver disease
- Increased metabolism of 25(OH)D_3
  - – Anticonvulsant therapy
- Decreased production of calcitriol
  - – Renal failure
  - – VDDR I
  - – Hyperphosphatemia
  - – Oncogenic osteomalacia
- Vitamin D resistance
  - – VDDR II

Relocation of circulating calcium
- Extravascular deposition
  - – Hungry bone syndrome
  - – Pancreatitis
  - – Osteoblastic metastases
- Intravascular binding
  - – Citrate, EDTA, acute respiratory alkalosis

Miscellaneous
- Sepsis
- Drugs
  - – Gentamycin, cisplatin, mithramycin, bisphosphonates, phosphate salts
- Hypoproteinemia

release of calcium from bone (see sections on phosphate and magnesium). Resistance to the actions of PTH will also result in hypocalcemia and can occur in pseudohypoparathyroidism, renal failure, and magnesium depletion (see section on phosphate).

Disorders of vitamin D metabolism will also result in hypocalcemia. Vitamin D regulates intestinal calcium absorption, skeletal responsiveness to PTH, and normal bone turnover. Thus, the pathogenesis of hypocalcemia may reflect one or more of these physiologic actions of vitamin D metabolites. Vitamin D deficiency may result from abnormalities at any point in its metabolic pathway, including diminished intake or intestinal absorption, reduced formation of the precursor in the skin, and impaired hydroxylation in the liver and kidney including hereditary deficiency of 1-α-hydroxylase (vitamin D-dependent rickets). Vitamin D resistance may also occur because of disorders of the vitamin D receptor leading to defective action on the target organs.

Relocation of circulating calcium which may occur in several clinical circumstances also causes hypocalcemia. Profound hypocalcemia associated with hypophosphatemia and hypomagnesemia may occur after surgical correction of primary or secondary hyperparathyroidism associated with severe osteitis fibrosa cystica. This condition, known as the hungry bone syndrome or recalcification tetany, results from rapid and excess bone mineralization over bone resorption [20]. The severity of hypocalcemia correlates well with the severity of bone disease before treatment. Predictors of its occurrence after surgery for primary hyperparathyroidism include more severe hypercalcemia, higher alkaline phosphatase and PTH levels, renal insufficiency, and larger parathyroid adenomas. Hypocalcemia occurs in 40 – 70% of patients with acute pancreatitis, likely due to calcium deposition in areas of fat necrosis [21]. Hyperphosphatemia may cause hypocalcemia by precipitation of calcium phosphate complexes in soft tissues and by inhibition of 1-α-hydroxylase, which results in decreased formation of 1-α,25-$(OH)_2D_3$. Inhibition of calcium re-

lease from bone by hyperphosphatemia may also contribute to hypocalcemia. Renal failure may be associated with hypocalcemia by several mechanisms, including hyperphosphatemia, impaired production of calcitriol because of the reduced renal mass, skeletal resistance to vitamin D and PTH, and metabolic acidosis.

Increased intravascular binding of calcium may also result in hypocalcemia. Infusion of citrate (given with blood transfusion) or ethylene diaminetetraacetic acid (EDTA) can chelate calcium in the blood, thereby reducing the ionized calcium concentration without affecting total calcium. A similar effect is induced by acute respiratory alkalosis, which enhances calcium binding to albumin.

Miscellaneous causes of hypocalcemia include hypoalbuminemia which results in reduced total calcium with normal ionized calcium, which alone is not clinically significant. Several drugs may be associated with hypocalcemia. The anticonvulsants phenobarbital and diphenylhydantoin cause hypocalcemia by inducing hepatic microsomal P450 oxidase activity, leading to accelerated metabolism of vitamin D_3 and $25(OH)D_3$ into polar, hydroxylated, and biologically inactive products [22]. Cisplantin causes hypocalcemia by inducing renal magnesium wasting and hypomagnesemia [23]. The incidence of hypocalcemia in the critically ill or postsurgical patient may approach 80 %. The vast majority of these cases are due to hypoalbuminemia, and the ionized calcium concentration is normal.

Clinical Manifestations of Hypocalcemia

The clinical manifestations of hypocalcemia depend partly on the underlying cause. They may be subtle (e.g. depression) or florid (e.g. tetany), and their severity is not closely related to the degree of hypocalcemia. Asymptomatic hypocalcemia may contribute to cardiac dysfunction, including hypotension and heart failure [24]. Profound hypocalcemia may not be associated with any symptoms, as in many patients with renal failure. The concurrent blood pH, as well as other electrolyte abnormalities, is likely to influence the symptoms.

– *Neuromuscular manifestations*
The classic manifestation of neuromuscular irritability in hypocalcemia is tetany. It usually begins with circumoral and acral paresthesias and may progress to the typical cramps in the muscles of the hands (main d'accoucheur, with adduction of thumbs and flexion of MCP joints), larynx (laryngismus), or elsewhere. Latent tetany may be detected by observing a facial twitch on tapping the branches of the facial nerve (Chvostek sign, present in 25% of normal adults), or by observing carpopedal spasm, which is produced after 3 minutes of inflation of a sphygmomanometer cuff above systolic pressure (Trousseau's sign, more specific, but can be negative in 30% of patients with latent tetany). Acidosis protects against tetany, while alkalosis facilitates tetany [25]. Correction of the metabolic acidosis in patients with renal failure and severe hypocalcemia may precipitate tetany. Seizures may be the presenting manifestation of hypocalcemia. Hypocalcemia may be associated with mental retardation in children and dementia in adults. The latter may improve considerably with correction of hypocalcemia. Reversible emotional instability, anxiety, confusion, hallucination, and psychosis may occur in hypocalcemia.

– *Cardiovascular, ectodermal, and gastrointestinal effects*
EKG manifestations of hypocalcemia include prolongation of the Q-T interval and nonspecific T wave changes. Coarse, dry, and scaly skin; brittle nails; and thin and sparse hair have all been observed after hypocalcemia. Children with hypoparathyroidism may exhibit dental aplasia, hypoplasia, or caries. Psoriasis and eczema can be exacerbated by hypocalcemia. Bilateral cataracts may also occur, and treatment of hypocalcemia arrests their progression.

Diagnostic Approach to Hypocalcemia

Once hypocalcemia has been found on routine laboratory testing or is suspected on a clinical basis, the initial step should be an assessment of the serum ionized calcium. Both the history and physical examination may be helpful in providing clues, such as possible surgical hypoparathyroidism, idiopathic hypoparathyroidism (e.g. candidiasis), pseudohypoparathyroidism (somatic features), vitamin D deficiency (diet and intestinal disease), and magnesium deficiency.

Determination of the PTH level helps distinguish PTH deficiency from conditions in which responsiveness to PTH is impaired. Measurement of serum vitamin D metabolite levels, especially 25(OH)D and calcitriol, may be of great value in differentiating the various forms of vitamin D deficiency and vitamin D resistance.

Treatment

Treatment of hypocalcemia depends on severity, rapidity of onset, the presence of symptoms, and the underlying cause. It should be emphasized that correction of the underlying disease is generally required for persistent normalization of the plasma calcium concentration.

Mild asymptomatic hypocalcemia (plasma ionized calcium > 3.2 mg/dL) is well tolerated and can be managed initially by increasing dietary calcium intake or by oral calcium supplements (250 to 500 mg elemental calcium every 6 hours). Symptomatic hypocalcemia should be treated as a medical emergency and requires parenteral calcium, which should be given with caution to patients receiving digitalis to prevent toxicity. Initial therapy consists of 1 – 2 ampules of calcium gluconate (90 mg of elemental calcium per 10-ml ampule) in 5 – 10 mL of 5% dextrose given over 5 – 10 minutes, repeated as needed. Slow administration is critical, because the rapid IV infusion of calcium can cause serious cardiac dysfunction, including systolic arrest. An infusion of elemental calcium at a rate of 0.5 – 1.5 mg/kg/hour should follow initial treatment. Intravenous calcium should be continued until the patient is on an effective regimen of oral calcium and vitamin D.

Hypocalcemia due to magnesium depletion requires parenteral magnesium sulfate. Hypocalcemia after parathyroidectomy may be severe and may result from the hungry bone syndrome (especially in patients with osteitis fibrosa cystica) [20]. Careful monitoring is required to prevent potentially serious complications; therefore, plasma calcium should be measured 2 – 4 times daily for the first few postoperative days. Oral calcium (2 – 4 g of elemental calcium [50 – 100 mmol]/day) should be given when the patient is able to swallow. Intravenous calcium is indicated if the patient develops tetany, latent tetany, or a plasma calcium concentration < 7.5 mg/dL (1.9 mmol/L). Massive and prolonged supplementation of calcium may generally be re-

quired (1 – 4 mg/kg/hour of elemental calcium given in 1 L of 5% dextrose, initiated at 40 – 50 mL/hour, and titrated according to the plasma calcium) to maintain the plasma calcium above 8 mg/dL. Calcitriol (oral or IV, 2.0 – 3.0 μg/day) should be initiated if the foregoing measures are not adequate. For patients on dialysis who are deemed to be at high risk for the hungry bone syndrome, IV calcitriol (2 μg at the end of each dialysis) started 3 – 5 days before parathyroidectomy and continued postoperatively may help prevent severe hypocalcemia. Management of chronic hypocalcemia in patients with relatively normal renal function requires therapy with oral calcitriol together with oral calcium supplements. Care should be taken to avoid severe hypercalciuria by maintaining serum calcium at the lower limits of normal. Thiazide diuretics with dietary salt restriction may be useful adjuncts to such therapy.

Hypercalcemia

Hypercalcemia is a relatively frequent medical problem. The prevalence and causes of hypercalcemia are distinctly different among individuals in the general population and hospitalized patients. The prevalence in the general population is up to 0.1%, but may be higher in the hospital inpatient population [26]. Among its many causes, by far the most common are malignancy and primary hyperparathyroidism, which together account for up to 80 – 90%. Among ambulatory outpatients with hypercalcemia, the vast majority have primary hyperparathyroidism, and prompt identification of hypercalcemia and its causes becomes of paramount importance in preventing the morbidity and mortality associated with this metabolic disorder.

Table 2. Causes of Hypercalcemia

Parathyroid-related
Primary hyperparathyroidism
Adenoma, hyperplasia, carcinoma
MEA
Type 1 and 2
FHH
Tertiary hyperparathyroidism
Malignancy-related
Humoral hypercalcemia of malignancy
Lung, breast, renal, esophagus, cervix, head and neck
Skeletal involvement
Myeloma, lymphoma, metastases
Vitamin D-related
Vitamin D intoxication
Granulomatous disorders
Sarcoidosis, histoplasmosis, tuberculosis
Drug-related
Lithium, thiazides, vitamin D, vitamin A, aluminum intoxication
Miscellaneous
Immobilization, postrenal transplantation, Milk alkali syndrome, hyperthyroidism, Paget's disease

The causes of hypercalcemia are shown in Table 2. Primary hyperparathyroidism may occur as often as 1 in 500 individuals and is most often benign. Approximately 85% of patients with primary hyperparathyroidism have single adenomas, 10 – 15% have diffuse hyperplasia, and < 5% have parathyroid carcinomas. The principal systems affected include the kidney, bone, CNS and gastrointestinal tract. Hypercalcemia results from increased bone resorption, increased intestinal absorption of calcium secondary to a PTH-induced increase in $1,25(OH)_2D_3$, and also to

increased renal reabsorption of calcium mediated by the increased PTH. Renal sequelae of PTH excess and hypercalcemia include nephrolithiasis (in 10 – 15% of cases), nephrocalcinosis, polyuria, dehydration, renal insufficiency, and, rarely, renal failure. Skeletal manifestations of hyperparathyroidism include diffuse osteopenia, subperiosteal bone resorption, endosteal erosion, cortical striations, osteosclerosis, "rugger jersey spine", and osteitis fibrosa cystica [27]. The latter lesion is classic for hyperparathyroidism, but is rare. Patients with significant skeletal involvement may have progressive bone pain and pathologic fractures. Gastrointestinal complications of hyperparathyroidism include peptic ulcer disease and pancreatitis. Hyperparathyroidism can also be found in patients with multiple endocrine adenomatosis (MEA). Werner's syndrome (MEA type I) consists of pancreatic and pituitary tumors associated with parathyroid adenomas. Pheochromocytomas and medullary carcinoma of the thyroid are found in MEA type II. This condition is associated with hyperparathyroidism in type II a or with mucosal neuromas in type II b. Both MEA I and II are inherited as autosomal dominant traits.

Familial hypocalciuric hypercalcemia (FHH) is characterized by hypercalcemia beginning in the first decade of life, low fractional urinary calcium excretion (a value < than 0.01 suggests FHH is present), a tendency to develop hypermagnesemia, normal renal function, and failure of hypercalcemia to be corrected by subtotal parathyroidectomy [28]. It is inherited as autosomal dominant trait. Whereas chronic hypercalcemia in primary hyperparathyroidism is associated with severe impairment in urine concentrating ability, patients with FHH and long-standing hypercalcemia do not display such an impairment [29]. The FHH gene has been localized to the long arm of chromosome 3. Recently, as described above, the gene encoding the calcium receptor, which is highly expressed in the kidney and parathyroid gland and functions to sense physiologically relevant changes in serum calcium, was localized to the FHH locus on chromosome 3, and mutations in this gene explain this syndrome [6]. The lack of defective urinary concentration in FHH patients is likely explained by the effects of the calcium-sensing receptor on the function of the thick ascending loop of Henle, and on water reabsorption in the collecting duct [30].

Malignancy-associated hypercalcemia is the most common paraneoplastic syndrome, occurring in up to 10% of all patients with cancer [31]. Of all patients with hypercalcemia and malignancy, 44% have hematologic and 41% have solid neoplasms. Hypercalcemia complicates 11% of all the hematologic neoplasms, but only 6% of patients with solid neoplasms are hypercalcemic [32]. The most common malignancies associated with this disorder are breast, renal cell, and lung cancers along with multiple myeloma and squamous cell carcinomas of the head and neck [33]. The malignancy is almost never occult at the time when patients show hypercalcemia, and the occurrence of hypercalcemia is usually a poor prognostic factor. An exception to this rule is multiple myeloma, in which hypercalcemia may be the presenting symptom of the disease and the course may be more chronic [34]. The mechanisms responsible for the hypercalcemia are both humoral and local, and include production of a parathyroid hormone-related protein (PTHrP) by tumor cells and release of bone resorbing cytokines and growth factors by tumor cells metastatic to bone with resultant osteolysis [31]. Ectopic production of authentic PTH by tumor cells, which is extremely rare, has been documented for small cell lung cancer, ovarian cancer, and a primitive neuroectodermal cancer with extensive metastasis [35]. Pa-

tients with multiple myeloma have cystic bone lesions. The mediators of increased osteoclastic bone resorption in multiple myeloma include the interleukins IL-2 and IL-6, and tumor necrosis factor (TNF).

Vitamin D-related hypercalcemia is due to increased intestinal absorption of calcium and to increased bone resorption and can be produced with the administration of large doses of vitamin D or any of its metabolites. Sarcoidosis and other granulomatous disorders are significant causes of hypercalcemia. Hypercalciuria is a common feature of sarcoidosis (35 – 40% of unselected patients), while the incidence of hypercalcemia ranges from 2 – 25% in several studies [36]. The abnormal calcium metabolism in sarcoidosis may be the result of either excessive endogenous production or an abnormal sensitivity to calcitriol, and both sun exposure and vitamin D therapy have provoked frank hypercalcemia in affected patients [37]. Other renal complications in these patients include nephrocalcinosis and nephrolithiasis. Renal involvement in sarcoidosis can progress to acute and chronic renal failure (coexisting hypercalcemia may accelerate development of the latter). Typically, patients with hypercalcemia have elevated levels of $1,25(OH)_2$ vitamin D and suppressed PTH levels [36]. The elevated plasma levels of $1,25(OH)_2D_3$ in sarcoidosis result from its increased production by the macrophage, a prominent constituent of the sarcoid granuloma that possesses $25(OH)D_3$-1-α-hydroxylase [38]. The 1-α-hydroxylation reaction in macrophages is inhibited by glucocorticoids, and this explains in part why these agents are the mainstay of therapy of sarcoid-induced hypercalcemia [39]. Other granulomatous disorders associated with hypercalcemia include tuberculosis, histoplasmosis, coccidiomycosis, berylliosis, and leprosy. Evidence suggests that the pathogenetic mechanism is similar to that in sarcoidosis.

Drug therapy, including vitamin D and vitamin A therapy, must also be considered in the differential diagnosis of hypercalcemia. Thiazide diuretics can be associated with hypercalcemia, particularly when an underlying condition may perpetuate the increase in serum calcium. The mechanisms include a thiazide-induced volume contraction that may increase renal reabsorption of calcium, and contraction metabolic alkalosis that may lead to increased calcium binding by proteins. A direct effect of thiazides on distal tubular calcium reabsorption has been shown in the rat, and, a direct effect of thiazides on bone has been shown in dogs [40]. The latter finding is supported by the thiazide-induced hypercalcemia observed in hemodialysis patients. Lithium therapy has been reported to result in hypercalcemia with high levels of circulating immunoreactive PTH levels [41]. Lithium may increase the threshold at which serum calcium suppresses PTH secretion. Also, lithium carbonate can produce hypocalciuria, probably mediated in part by excess PTH secretion or direct enhancement of tubular calcium reabsorption. Calcium carbonate and acetate therapy in large doses, used as phosphate binders in patients undergoing dialysis, can lead to hypercalcemia. This tendency is accelerated in patients undergoing dialysis who have aluminum-induced low-turnover bone disease. Hypercalcemia can occur in these patients with or without the concomitant administration of calcitriol.

Additional causes of hypercalcemia include immobilization, especially in children, and Paget's disease patients in whom bone turnover is increased [42]. Hyperthyroidism may also be associated with hypercalcemia. Post-transplantation hypercalcemia with elevated serum PTH after successful renal transplantation can occur in 8 – 35% of cases [43]. Typically, hypercalcemia disappears within 6 months after transplantation but may last as

long as 24 months. Other contributing factors include osteomalacia, phosphate depletion, and the use of steroids and diuretics. The milk-alkali syndrome is characterized by hypercalcemia, metabolic alkalosis, and renal insufficiency. Hypercalcemia is caused by the ingestion of large quantities of calcium, which leads to increased serum calcium, together with the ingestion of alkali, which increases protein-bound calcium and renal reabsorption of calcium. Hyperphosphatemia may develop in this syndrome because of either the high phosphate content of milk or the concomitant renal insufficiency. The combination of hypercalcemia and hyperphosphatemia in the face of metabolic alkalosis may produce metastatic calcification and further renal damage. Dietary modifications are an essential part of therapy for this syndrome.

Consequences of Hypercalcemia

The clinical manifestations of hypercalcemia are influenced by the degree of hypercalcemia and the rate of onset. The clinical spectrum of hypercalcemia ranges from the asymptomatic patient found on a routine serum analysis to the patient with hypercalcemic crisis who presents in coma. The clinical manifestations of hypercalcemia reflect disturbances in gastrointestinal, cardiovascular, renal, and CNS function. CNS manifestations can range from subtle alterations in personality to acute psychosis. Specific manifestations include depression, bizarre behavior, apathy, drowsiness, memory impairment, obtundation, or even coma. Increased calcium in cerebrospinal fluid has been alleged to decrease the conduction of nerve terminals. Cardiovascular manifestations of hypercalcemia reflect the fact that calcium is an important regulator of excitation-contraction coupling of the heart and of smooth muscle tension in peripheral vessels. It exerts a positive inotropic effect on the heart and reduces heart rate, similar to the effect of cardiac glycosides. Hypercalcemia causes shortening of the Q-T interval in the EKG. Calcification of cardiac valves and narrowing of coronary arteries as well as extensive pulmonary calcification has been reported in chronic hypercalcemia. Renal manifestations include impairment of renal function as a result of decreased renal blood flow (RBF) and GFR. Impairment of sodium reabsorption, which results from inhibition of Na^+-K^+-ATPase in the thick ascending limb and distal tubules, leads to volume contraction in hypercalcemia [44]. Polyuria results from impairment of the renal concentration capacity, which may be mediated by the calcium-sensing receptor [30]. Calcium nephropathy, which presents clinically as interstitial nephritis, results from calcium deposition and interstitial inflammation.

Gastrointestinal manifestations include constipation, nausea, vomiting, and anorexia. Duodenal ulcer disease occurs in 10 – 20% of patients with hypercalcemia. Pancreatitis can occur in as many as 35% of patients in acute hypercalcemic crisis. Metastatic calcification of soft tissue may give rise to nephrocalcinosis and calcification of pancreatic ducts, gastric mucosa, intima or media of blood vessels, joint cartilage (chondrocalcinosis), cornea and conjunctiva (band keratopathy), skin, heart, lung, or other locations.

Diagnostic Approach to Hypercalcemia

Several principles guide the approach to the hypercalcemic patient. First, a PTH level elevated above the normal range in a patient with hypercalcemia is almost always indicative of primary hyperparathyroidism. Second, the number of patients with malignancy and ele-

vated PTH caused by ectopic production of authentic PTH is exceedingly small and is far fewer than the number of patients with coexistent malignancy and hyperparathyroidism. Third, malignancy-associated hypercalcemia is rarely the only manifestation of underlying malignancy. Fourth, the clinically asymptomatic patient with hypercalcemia detected by an autoanalyzer will almost always have primary hyperparathyroidism. Vitamin D or A intoxication, granulomatous diseases, milk-alkali syndrome, and other causes for hypercalcemia are usually obvious by initial history and physical examination.

With these principles in mind, the following approach is suggested. All patients with hypercalcemia should undergo a complete history and physical and routine laboratory studies including radiography of the chest and urinalysis. Any abnormality or organ-specific symptom complex should be further evaluated to rule out the presence of malignancy. In the absence of detectable malignancy, a PTH level should be obtained. A distinctly elevated midregion or intact PTH should be considered as evidence of primary hyperparathyroidism. If the PTH level is within the normal range, the diagnosis could still be hyperparathyroidism, but other known causes of hypercalcemia should be reviewed and other diagnostic tests considered based on suggestive clues in the history and physical. A urine calcium-to-creatinine ratio should be obtained to rule out familial hypocalciuric hypercalcemia. The presence of osteitis fibrosa, albeit rare, indicates hyperparathyroidism. An elevated level of 25(OH) vitamin D indicates vitamin D intoxication. In hypercalcemic patients without symptoms and with a normal serum PTH level and normal laboratory evaluation, the approach should be careful follow-up with repeated PTH measurements. If the PTH level is low and malignancy is not evident, and milk-alkali syndrome and vitamin D intoxication are unlikely because of history and physical exam, granulomatous diseases should be considered. Elevated angiotensin-converting enzyme and $1,25(OH)_2$ vitamin D levels and suppression of the hypercalcemia with steroids support the diagnosis of sarcoidosis.

Treatment of Hypercalcemia

The magnitude of the hypercalcemia is a key consideration in determining the need for immediate, aggressive therapy. On the basis of the serum calcium concentration alone, hypercalcemia may be classified as mild (< 12 mg/dL) moderate (12 – 15 mg/dL) or severe (> 15 mg/dL). In moderate and severe hypercalcemia, the serum calcium must be reduced expeditiously yet safely while diagnostic efforts are in progress and in preparation for definitive therapy. There are 4 basic goals for the therapy of hypercalcemia: 1) to correct dehydration, 2) to enhance the renal excretion of calcium, 3) to inhibit accelerated bone resorption, and 4) to treat the underlying disorder.

General measures include the intravenous administration of isotonic saline as the first step in the management of severe hypercalcemia. When the depleted intravascular volume is restored to normal, the serum calcium concentration should decline, at least by the degree to which dehydration raised it. The reduction usually amounts to 0.40 – 0.60 mmol/L (1.6 – 2.4 mg/dL), but hydration alone rarely leads to normalization of the serum calcium concentration in patients with severe hypercalcemia. The expansion of intravascular volume is also helpful because it increases renal calcium clearance by several mechanisms. First, the increase in the GFR leads to increased filtration of calcium. Second, proximal tubular sodium and calcium reabsorption decreases as the GFR increases.

Third, as more sodium and water are presented to distal renal tubular sites, an obligatory calciuresis ensues. The rate of saline administration should be based on the severity of the hypercalcemia, the extent of dehydration, and the tolerance of the cardiovascular system for volume expansion. A widely used regimen is to administer 2.5 – 4 L of isotonic saline daily, recognizing the need to adjust the rate of fluid administration or to administer a diuretic agent if symptoms and signs of fluid overload appear. Intake should be greater than output by at least 2 L in the first 24 hours.

In addition to hydration with saline, adjunctive therapy with a loop diuretic may be indicated to facilitate urinary excretion of calcium. Loop diuretics enhance the calciuric effects of volume expansion by inhibiting calcium reabsorption in the thick ascending limb of the loop of Henle. Thiazide diuretics should never be used in this situation because they enhance distal tubular reabsorption of calcium and thus may actually exacerbate hypercalcemia. Volume expansion must precede the administration of furosemide, because the effect of the drug depends on the delivery of calcium to the ascending limb. Intensive administration of furosemide (40 – 80 mg intravenously every 1 – 2 hours) with fluid and electrolyte replacement based on urinary losses is an effective regimen for the treatment of hypercalcemia. This aggressive approach will lead to marked hypercalciuria, but it requires frequent measurement of water and electrolyte excretion.

Four agents lower plasma calcium concentration by blocking osteoclast function: calcitonin, bisphosphonates, mithramycin, and gallium nitrate. Salmon calcitonin decreases serum calcium, predominantly by reducing bone resorption and less importantly by enhancing urinary calcium excretion. It can be given intramuscularly or subcutaneously in a dose of 4 – 8 U/kg twice a day. It is safe and nontoxic and when effective, works very rapidly to lower the plasma calcium concentration by a maximum of 1 – 2 mg/dL beginning within 2 – 3 hours [45]. Rapid loss of the effect of calcitonin can occur after 24 – 72 hours of treatment. This abolition of hypocalcemic action has been referred to as the "escape" phenomenon, which can be partly explained by down-regulation of hormone receptors, as well as by uncoupling of receptors from adenylate cyclase.

Mithramycin inhibits DNA-dependent RNA synthesis in osteoclasis. A dose of 25 μg/kg of body weight is infused in D5W over a period of 4 – 8 hours. The plasma calcium concentration begins to fall within about 12 hours and usually reaches a nadir by 48 hours. The hypocalcemic effect lasts for several days with repeated doses given at 3 – 7 day intervals [46]. Side effects include nausea, vomiting, anorexia, bone marrow suppression, and a bleeding phenomenon attributable to thrombocytopenia or decreased platelet function. Hepatoxicity and nephrotoxicity can also occur and toxicity is more likely to occur in patients with renal insufficiency because its excretion is largely renal. For these reasons, it is reserved for patients with severe malignancy-associated hypercalcemia who do not respond to other modalities, including a bisphosphonate.

Bisphosphonates are synthetic analogues of pyrophosphate not rapidly hydrolyzed in vivo. Their great affinity for bone and resistance to degradation account for their extremely long half-life in bone. They are excreted unchanged by the kidney. Their absorption from the gastrointestinal tract is generally poor, averaging < 10%, particularly when given with food. These agents inhibit osteoclastic bone resorption and retard (in a dose-dependent manner) the deposition of hydroxyapatite in bone collagen thereby increasing unmineralized osteoid and inhibiting

the formation of calcium phosphate crystals at higher doses. They are relatively nontoxic and are very useful in the management of moderately severe hypercalcemia [47]. The maximum effect is usually not seen for several days, so these agents are usually given with more rapidly acting modalities such as saline and calcitonin. Rarely, a significant response and even hypocalcemia can be seen within the first 24 hours. The bisphosphonates available in the United States are etidronate, pamidronate, and alendronate. Other bisphosphonates currently being developed or in the process of getting FDA approval, include ibandronate, tiludronate, and residronate. Pamidronate is more potent than etidronate and may produce a longer hypocalcemic response; it is probably the bisphosphonate of choice [47]. The usual IV dose varies with the degree of hypercalcemia. Up to 90 mg may be given usually as a single IV infusion over 4 or 24 hours, both of which appear to be equally effective. An oral regimen of 1200 mg daily for up to 5 days is also available. The dose should not be repeated until after a minimum of 7 days. This regimen is well tolerated and has minimal adverse effects, which include a mild transient fever, transient leukopenia, and a small reduction in serum phosphate levels.

Gallium nitrate is also useful for parenteral therapy of hypercalcemia. It appears to inhibit bone resorption by adsorbing to and reducing the solubility of hydroxyapatite crystals [48]. It has an additional effect of inhibiting PTH secretion in vitro; it may therefore be particularly effective in the treatment of hypercalcemia resulting from hyperparathyroidism. It is administered as a continuous IV infusion (200 mg/m^2 of BSA in 1 L of fluid daily for 5 days).

Because enhanced absorption of dietary calcium is primarily responsible for the hypercalcemia associated with excess vitamin D administration or with the endogenous overproduction of calcitriol, such as is seen in chronic granulomatous diseases and in occasional cases of malignant lymphoma, dietary calcium should be restricted in these cases. Glucocorticoids may also inhibit intestinal calcium absorption. The effect of steroids in the hypercalcemia of malignancy (usually hematologic) may be mediated through inhibition of osteoclastic bone reabsorption, cytolysis of tumor cells, and inhibition of prostaglandin synthesis.

Oral phosphate can decrease intestinal calcium absorption by forming insoluble calcium phosphate complexes both in the intestine and also in the plasma, thereby lowering the plasma calcium concentration. The risk of tissue calcium phosphate deposition, appears to be a limiting factor for the use of oral phosphate. This is a major concern with the use of IV phosphate, which is used only for severe, life-threatening hypercalcemia for which all other measures have failed, The usual dose is 250 mg qid, which can be increased to 500 mg qid, if severe diarrhea does not develop.

Chelation of ionized calcium using EDTA or IV phosphate has the advantage of almost immediate onset of action. However, toxicity limits the use of these agents to life-threatening refractory hypercalcemia. EDTA can cause acute renal failure (ARF), while phosphate therapy may lead to calcium phosphate precipitation in the tissues, potentially causing acute or chronic renal failure, vascular calcifications, and occasionally life-threatening arrhythmias. Hemodialysis with low or zero calcium dialysate and peritoneal dialysis (although slower) are both very effective modes of therapy. Dialysis is particularly useful in patients with renal insufficiency or congestive heart failure who cannot safely be given a saline load. However, rebound hypercalcemia may occur rapidly after cessation of therapy. Hemodialysis is the most effective

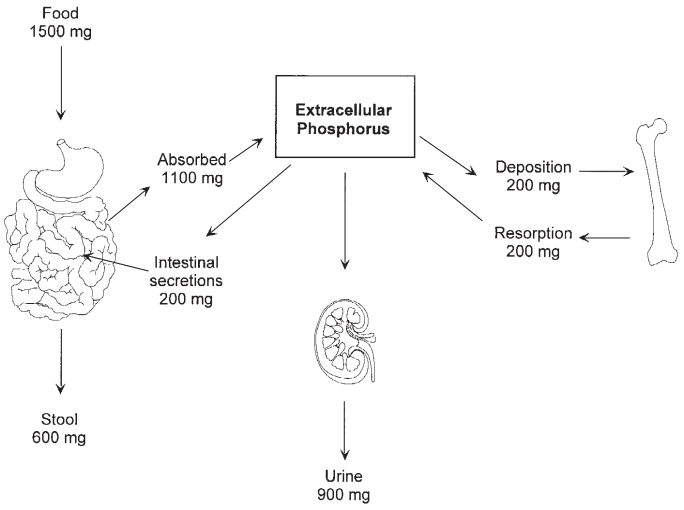

Figure 3. Normal phosphate homeostasis.

therapy for patients with severe hypercalcemia in the presence of end-stage renal disease (ESRD). Hourly removal of calcium is approximately twice that reported with saline and furosemide. It is advisable to perform hemodialysis under cardiac monitoring when using zero or low calcium dialysate.

Phosphorus

Normal Phosphate Homeostasis

The normal human body contains approximately 700 g, of phosphorus, of which 85% is contained within the bone mineral, 14% is present within the cells, and 1% is in the extracellular fluid [49, 50]. Most intracellular phosphorus is present as organic phosphate compounds which are necessary for the maintenance of cellular integrity and metabolism. Although the amount of inorganic phosphate in the cell is relatively small, it plays a critical role in cellular function because it constitutes a major source of phosphorus for the synthesis of ATP.

Plasma phosphorus concentration in adults is maintained between 2.5 and 4.5 mg/dL. The kidney and the gastrointestinal tract are the 2 major organ systems involved in maintaining phosphorus homeostasis. While phosphate absorption by the intestine may intermittently provide the extracellular fluid with a phosphate load, the kidney continuously maintains phosphate homeostasis by excreting the precise amount absorbed in excess of the body requirements. In the steady state, urinary phosphate excretion reflects the amount of phosphate absorbed by the intestine. As shown in Figure 3, the average daily intake of phosphorus is 1,500 mg, of which two-thirds is absorbed mainly in the duodenum and jejunum, and one-third is excreted in the stool. Intestinal secretions contain approximately 200 mg of phosphorus that re-enters the intestinal lumen. Approximately 200 mg of phosphorus enters and leaves the bone each day. Thus, the net intestinal absorption of phosphate is approximately 900 mg, which is excreted by the kidneys.

Intestinal Phosphate Transport

The majority of phosphate absorption takes place in the duodenum and jejunum, although the ileum and colon can absorb smaller amounts of phosphate. In normal individuals, there is a linear relationship between net phosphate absorption and dietary phosphorus intake. Intestinal phosphate absorption takes place via 2 mechanisms: 1) a diffusional process via the paracellular pathway and 2) a cellularly mediated active transport. Under normal circumstances, intestinal phosphate absorption occurs almost entirely through the diffusional process, which explains the observation that net phosphate absorption in humans is a linear function of dietary phosphate intake. Thus, the fractional absorption of phosphate from the intestine remains constant over a wide range of phosphate intake. The active component is likely to play an important role only under extreme circumstances such as severe dietary phosphate deprivation [49].

The cellularly-mediated active transport of phosphate involves sodium-dependent entry through a sodium-phosphate cotransporter in the brush border membrane. The active component of phosphate absorption is regulated by a variety of hormonal and non-hormonal factors including calcitriol. Although calcitriol increases both calcium and phosphate absorption in the intestine, different cellular mechanisms are involved in each case; thus, intestinal phosphate absorption is not necessarily coupled with calcium absorption. Other hormones that may enhance intestinal absorption of phosphate include PTH, thyroxine, estrogens, growth hormone, calcitonin, and glucocorticoids. PTH and estrogens may act mostly by increasing the synthesis of calcitriol. The mechanisms by which the other hormones affect phosphate absorption remain unclear. Nonhormonal factors may also regulate active phosphate transport. Variations in dietary phosphate intake can alter sodium-dependent phosphate transport; however, this effect is likely mediated by changes in calcitriol levels resulting from the effects of phosphorus on 1-α–hydroxylase in the kidney. The presence of aluminum in the intestinal lumen decreases phosphate absorption. Likewise, calcium-rich diets will impair phosphate uptake by the intestine.

Renal Handling of Phosphate

As already discussed, the kidney is the principal organ involved in the regulation of phosphate homeostasis. Most circulating inorganic phosphorus is ultrafiltrable. Factors that alter urinary phosphate excretion do so by changing either the filtered load or the tubular reabsorption of phosphate, because little phosphate is secreted by the kidney. Approximately 80% of the filtered load is reabsorbed by the renal tubules. Tubular reabsorption of phosphate and its regulation are determined by specific cellular events localized mostly in the proximal tubule, where 60 – 70% of renal reabsorption of phosphate takes place. Significant phosphate reabsorption occurs between the early distal tubule and the final urine. Although little is known about the mechanisms involved, there is evidence for regulated phosphate reabsorption in the distal nephron [49, 50].

– *Cellular mechanisms for proximal tubular phosphate transport*
  The transport of phosphorus in the proximal tubule is largely transcellular. It involves uptake across the brush border membrane, translocation across the cell, and efflux across the basolateral membrane. The uptake of phosphorus across

the brush border membrane is mediated by the sodium phosphate cotransporter and depends on the sodium gradient maintained by the basolateral Na-K-ATPase. Much has been learned about the nature of the sodium-phosphate (NaPi) cotransporter following its cloning in several species [51]. Once inside the cell, phosphorus may be incorporated into several organic compounds or extruded at the basolateral membrane. Little is known about the mechanisms involved in phosphate transport across the cell. At the basolateral membrane, the electrochemical gradient favors the extrusion of phosphate; however, diffusion across the basolateral membrane is limited to avoid depletion of cytosolic phosphate. Phosphate transport across the basolateral membrane appears to occur primarily by sodium-independent anion exchange mechanisms, which remain poorly understood.

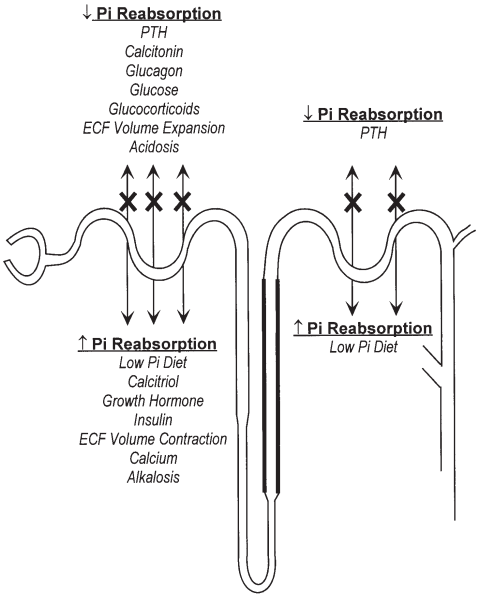

Figure 4. Tubular phosphate reabsorption.

– *Factors influencing renal handling of phosphate*

The overall tubular reabsorption of phosphate is controlled by a variety of dietary, metabolic, and hormonal factors as shown in Figure 4. Of these, PTH and dietary intake of phosphate primarily determine renal tubular phosphate reabsorption. The kidney responds to alterations in the filtered load of phosphorus by altering the excretion of phosphorus in the urine as appropriate. Urinary phosphate excretion decreases markedly in response to dietary phosphorus restriction. The adaptation of the renal tubule to dietary phosphate appears to involve alterations in Na^+-dependent phosphate transport, as suggested by studies demonstrating changes in NaPi cotransporter messenger RNA (mRNA) and protein induced by changes in dietary phosphate intake [52 – 54]. Furthermore, vitamin D metabolites may also contribute to the adaptive response to dietary phosphate restriction. The enhanced phosphate transport observed in phosphate depletion is resistant to phosphaturic agents such as PTH and calcitonin [55, 56], indicating that phosphate deprivation is a powerful stimulus for renal tubular phosphate reabsorption.

PTH is the major regulator of phosphate reabsorption by the kidney. PTH administration causes phosphaturia, and parathyroidectomy causes a decrease in urinary phosphate excretion. The primary site of action of PTH on phosphate transport is the proximal convoluted tubule and the proximal straight tubule. There is also evidence demonstrating PTH-sensitive phosphate transport in the distal nephron. The effects of PTH at the cellular

level are mediated by the PTH/PTHrP receptor located on the cell surface, which activates both adenylate cyclase and phospholipase C [57]. The effect of PTH to decrease phosphate reabsorption is thought to be largely mediated by cAMP; however, the protein kinase C pathway has also been implicated [58 – 61]. PTH has been shown to decrease NaPi cotransporters within the apical membrane resulting in decreased phosphate transport, and it has been suggested that exposure to PTH causes internalization of NaPi cotransporters by activation of endocytic mechanisms [62, 63]. The phosphaturic effect of PTH can be modified by a variety of factors. As discussed above, the increased phosphate reabsorption induced by dietary phosphate restriction can override the phosphaturic action of PTH.

Other hormones may also affect tubular phosphate reabsorption. The effect of vitamin D_3 metabolites on renal phosphate handling remains controversial. In general, acute administration of these agents is antiphosphaturic. The recent finding of vitamin D responsive elements in the Na-Pi promoter supports a direct role of vitamin D in phosphate reabsorption [64]. The antiphosphaturic effect of vitamin D may also be influenced by changes in serum calcium and PTH. Increased tubular reabsorption by growth hormone has also been recognized. Calcitonin has been shown to inhibit tubular phosphate reabsorption; however, the physiologic importance of this effect is not clear. Insulin and the insulin-like growth factors may also modulate phosphate transport. Insulin has modest antiphosphaturic effects. It has been shown to directly stimulate phosphate uptake by proximal tubules. Glucagon and glucose are both phosphaturic. The effect of glucose may be partially due to the concomitant osmotic diuresis, which inhibits proximal tubule transport. Glucocorticoids may cause phosphaturia independently of PTH. The effect of glucocortoids appears to be mediated by glucocorticoid receptors in the proximal tubule [1, 65].

Hypercalcemia has both direct and indirect effects that may contribute to increased phosphate reabsorption. The indirect effects include changes in GFR, RBF, and Kf, as well as changes in PTH levels which have profound effects on tubular phosphate handling. In addition, calcium has been shown to directly increase phosphate transport. Extracellular fluid volume expansion results in increased phosphate excretion, whereas volume contraction decreases phosphate excretion. Although the effects of volume status on tubular phosphate transport may be indirect, evidence suggests that volume expansion directly inhibits phosphate reabsorption independent of filtered load, plasma calcium, and PTH. Acid-base status can also influence renal phosphate handling. In general, acidosis is associated with decreased phosphate reabsorption, whereas alkalosis increases phosphate reabsorption; however, differences in phosphate transport also depend on whether the changes in acid-base status are acute or chronic. Diuretic agents such as acetazolamide and loop diuretics may decrease phosphate reabsorption. Phosphatonin, an as yet uncharacterized factor, has been implicated in the hyperphosphaturia of patients with X-linked hypophosphatemia and oncogenic osteomalacia [66, 67].

Hyperphosphatemia

The signs and symptoms of hyperphosphatemia are mostly related to the associated hypocalcemia and soft tissue calcification. The hypocalcemia may or may not be accompanied by tetany. Possible mechanisms for the decrease in serum calcium include deposition of calcium-phosphate salts in the soft tissues

and decreased production of calcitriol. Soft tissue calcification may occur when the calcium × phosphate product is > 70, especially in tissues with high pH, because the solubility of calcium-phosphate is lower in alkaline pH. Thus, the conjunctiva and the lung are at risk for calcium-phosphate precipitation because outward diffusion of carbon dioxide allows the local pH to increase. Consequently, band keratopathy and pulmonary calcifications may occur. ARF with intratubular precipitation of calcium and phosphorus may occur following a phosphate load. In chronic renal failure, hyperphosphatemia may lead to soft tissue calcification in the kidney, which in turn may accelerate the progression of renal failure [68]. Hyperphosphatemia plays a critical role in the development of secondary hyperparathyroidism in chronic renal failure.

Table 3. Causes of Hyperphosphatemia

Increased phosphate load	
Exogenous	
	Oral ingestion
	Vitamin D intoxication
	Intravenous administration
	Blood transfusions
	White phosphorus burns
Endogenous	
	Acidosis
	Tumor lysis syndrome
	Hemolysis
	Rhabdomyolysis
	Malignant hyperthermia
Decreased urinary excretion	
Decreased GFR	
	Acute renal failure
	Chronic renal failure
Increased tubular reabsorption	
	Hypoparathyroidism
	Pseudohypoparathyroidism
	Hyperthyroidism
	Acromegaly
	Postmenopausal state
	Glucocorticoid withdrawal
	Tumoral calcinosis
	Bisphosphonates

Causes of Hyperphosphatemia

As shown in Table 3, the causes of hyperphosphatemia can be grouped into 2 major categories: 1) increased phosphate load and 2) decreased urinary excretion. Pseudohyperphosphatemia may occur in hyperproteinemic states such as multiple myeloma, as well as in patients with hyperlipidemia, depending on the method used to measure phosphorus.

– *Increased phosphate load*
An increased phosphate load can result from either exogenous or endogenous sources. Under normal circumstances, the hyperphosphatemia is usually mild unless significant renal insufficiency or increased renal phosphate reabsorption coexist. The gastrointestinal tract is a common route of entry for exogenous phosphorus. Thus, dietary supplementation of phosphorus, particularly in combination with vitamin D, as well as phosphate-containing enemas may result in hyperphosphatemia. Likewise, hyperphosphatemia may result from the intravenous administration of phosphorus, and it usually occurs during the treatment of hypophosphatemia when the tubular reabsorptive mechanisms are adjusted to retain nearly all the filtered phosphate. Blood transfusions and infusions of lipid emulsions for total parenteral nutrition may also produce hyperphosphatemia. Phosphorus can be absorbed from the

skin, and hyperphosphatemia may develop in white phosphorus burns.

Hyperphosphatemia from endogenous sources may be caused by a shift of phosphate from intracellular stores or by a release of phosphate from the cells following tissue necrosis. Acidosis, particularly organic acidosis, may promote shifts of phosphate from the cells. The mechanism may involve the breakdown of organic phosphate with a release of inorganic phosphate into the extracellular fluid. Elevations in lactic acid are implicated in the hyperphosphatemia that may accompany major abdominal and thoracic surgery, as well as that associated with strenuous exercise. Respiratory acidosis may also lead to hyperphosphatemia. The mechanism appears to involve the decrease in intracellular pH that inhibits glycolysis, and the resultant decreased incorporation of inorganic phosphate into organic compounds leads to an increase in the efflux of phosphate from the cells.

Severe hyperphosphatemia may occur following significant tissue damage such as that seen in the tumor lysis syndrome, which occurs following chemotherapy for various malignancies, particularly lymphomas and leukemias. Acute hemolysis and rhabdomyolysis can both result in hyperphosphatemia. The hyperphosphatemia associated with malignant hyperthermia may be partially due to rhabdomyolysis.

– *Decreased urinary excretion of phosphate*

Reduced clearance of phosphorus may result from a decrease in GFR or from enhanced tubular phosphate reabsorption. Both acute and chronic renal failure can result in hyperphosphatemia. Several metabolic consequences of chronic renal failure prevent the development of significant hyperphosphatemia. These include increased PTH levels and low levels of calcitriol which decrease phosphate reabsorption. With progressive decline in GFR, however, hyperphosphatemia eventually develops.

Increased tubular reabsorption of phosphorus may occur in a variety of conditions, but it is most commonly seen in a spectrum of disorders characterized by PTH deficiency or resistance. The most common cause of hypoparathyroidism is surgical removal of the parathyroid glands, which often occurs in association with thyroid surgery, parathyroidectomy, or radical neck resections. Therapy with radioactive iodine may also result in hypoparathyroidism. Parathyroid insufficiency can also result from infiltrative processes involving the parathyroid gland, such as metastatic carcinoma and hemochromatosis. Hypoparathyroidism may be part of autoimmune endocrine failure. Hereditary hypoparathyroidism may occur in isolation or in association with Di George syndrome, characterized by defective development of the thymus, mucocutaneous candidiasis, and cardiac abnormalities.

End-organ resistance to PTH results in pseudohypoparathyroidism which involves a variety of disorders with biochemical features of hypoparathyroidism, including hyperphosphatemia and hypercalcemia, but usually with increased levels of PTH. Patients with type I pseudohypoparathyroidism (Albright hereditary osteodystrophy) have low urinary cAMP levels and phosphate excretion in response to PTH. About two-thirds of the patients with type I pseudohypoparathyroidism have somatic abnormalities as

originally described by Fuller Albright in 1942, including a short neck, round face, and shortening of the metacarpals and metatarsals. The underlying defect in type I pseudohypoparathyroidism involves the PTH receptor-cAMP generating system, and 3 types have been described: 1) type Ia is due to abnormalities of the guanine nucleotide-binding stimulatory protein [69 – 71], 2) type Ib may involve abnormalities of PTH receptor expression or function [72], and 3) type 1c is due to abnormalities of the adenylate cyclase catalytic subunit [73]. The majority of patients with somatic abnormalities have a defect in guanine nucleotide regulatory protein and, as expected, they have multiple endocrinologic defects, including hypothyroidism and gonadal dysfunction [74]. Patients with type II pseudohypoparathyroidism have high urinary cAMP but low phosphate excretion in response to PTH. Thus, in contrast to type I pseudohypoparathyroidism in which the defect is proximal to the generation of cAMP, in type II pseudohypoparathyroidism the defect is distal to the generation of cAMP. Patients with pseudohypoparathyroidism and renal tubular resistance to PTH may have normal response to the hormone at the level of the bone. Thus, these patients have somatic features of pseudohypothyroidism and hyperphosphatemia; however, they have bone changes of osteitis fibrosa.

Hyperphosphatemia may occur in association with hyperthyroidism and acromegaly. The cause of hyperphosphatemia in hyperthyroidism is likely due to a combination of factors, including increased intestinal absorption, increased bone resorption, and increased tubular reabsorption of phosphate. The mechanisms involved in the increased phosphate transport in hyperthyroidism are poorly understood. Growth hormone decreases phosphate excretion in humans. During menopause, low levels of estrogen and elevated levels of growth hormone are associated with hyperphosphatemia, which appears to result from increased tubular reabsorption of phosphate. Glucocorticoids inhibit sodium-dependent phosphate uptake by renal proximal tubular cells, and glucocorticoid withdrawal has been associated with hyperphosphatemia [75].

Tumoral calcinosis is a familial disorder associated with increased tubular reabsorption of phosphate These patients have hyperphosphatemia and calcifications in soft tissues and around large joints. PTH levels and PTH responsiveness are both normal. The exact mechanisms involved in the increased phosphate reabsorption in this syndrome are not clear. Bisphosphonate treatment of patients with Paget's disease has been associated with increased tubular reabsorption of phosphate and hyperphosphatemia [76].

Management of Hyperphosphatemia

The treatment of hyperphosphatemia should be aimed not only at the removal of phosphate from the circulation, but also at prevention [77]. Prevention includes eliminating exogenous or endogenous phosphate sources, as well as maintaining renal function. Thus, in patients receiving therapy for lymphoma who are at high risk for developing the tumor lysis syndrome, prevention of uric acid nephropathy by the administration of allopurinol and the maintenance of an alkaline diuresis may prevent severe hyperphosphatemia. Induction of an alkaline diuresis may also protect renal function and prevent severe hyperphosphatemia in patients with

rhabdomyolysis. In chronic renal failure, dietary phosphate restriction and the use of phosphate-binding antacids to impair intestinal phosphate absorption are commonly used to prevent hyperphosphatemia. In patients with severe hyperphosphatemia and dangerously elevated calcium-phosphate product, dialysis offers a means of removing phosphorus from the circulation.

Hypophosphatemia

Hypophosphatemia is a relatively common finding in hospitalized patients. A patient might have low serum levels of phosphorus with little deviation from normal in intracellular phosphorus (p-deprivation), or there might be low serum levels with low intracellular phosphorus (p-depletion). The latter represents a clinically very serious abnormality and is associated with numerous complications and organ abnormalities. In view of the important role of phosphorus as a source of energy, virtually all organ systems are affected in severe hypophosphatemia [49, 50]. Three basic underlying mechanisms affect cellular function in hypophosphatemia. First, severe hypophosphatemia results in decreased levels of erythrocyte 2,3-diphosphoglycerate (DPG), which increases the affinity of hemoglobin for oxygen, thus impairing oxygen release at the tissue level. Second, low levels of inorganic phosphate in the cell impair the synthesis of high-energy phosphate compounds such as ATP. And third, deficiency of intracellular organic phosphate may impair glycolysis. Thus, the manifestations of hypophosphatemia may involve a variety of organ systems; however, symptoms usually do not develop until the serum phosphorus level is < 1 mg/dL. Severe hypophosphatemia can affect the CNS and lead to a metabolic encephalopathy. The cardiopulmonary system can also be affected with impaired myocardial contractility leading to congestive heart failure (CHF) and weakness of the diaphragm resulting in respiratory failure. In bone, hypophosphatemia results in increased release of calcium from the bone and hypercalciuria. Prolonged hypophosphatemia may lead to a mineralization defect resulting in rickets and osteomalacia. Hypophosphatemia can affect both skeletal and smooth muscle with the latter resulting in ileus and dysphagia. Skeletal muscle dysfunction can present as a proximal myopathy or rhabdomyolysis. The hematopoietic system may also be affected by hypophosphatemia in the form of hemolysis, impaired phagocytosis and chemotactic activity, as well as thrombocytopenia.

Causes of Hypophosphatemia

As shown in Table 4, the mechanisms underlying hypophosphatemia can be grouped into three categories:

- decreased intestinal absorption of phosphorus,
- shifts of phosphorus into cells, and
- increased renal excretion of phosphate.

These mechanisms may occur singly or in combination. If none of the above mechanisms is present, pseudohypophosphatemia should be suspected, which is usually due to factors such as mannitol administration and hyperbilirubinemia that interfere with the assay used to measure serum phosphorus.

- *Decreased intestinal absorption of phosphate*
  Hypophosphatemia may occur in malnourished or starved patients who ingest

Table 4. Causes of Hypophosphatemia

Decreased intestinal absorption	
	Decreased dietary intake
	Vitamin D deficiency
	Phosphate binding antacids
	Vomiting
	Malabsorption
	Chronic alcoholism
Shift of phosphorus into cells	
	Respiratory alkalosis
	Carbohydrate load
	Nutritional recovery syndrome
	Recovery from hypothermia
	Hungry bone syndrome
Increased renal excretion	
	Hyperparathyroidism
	Malignancy
	Vitamin D deficiency
	XLH
	VDDR
	HHRH
	Idiopathic hypercalciuria
	X-linked nephrolithiasis with RF
	Fanconi syndrome
	Postrenal transplantation
	Metabolic acidosis
	Diuretics

a diet high in carbohydrates and deficient in phosphorus. Phosphorus-deficient diets are more likely to result in the development of hypophosphatemia in children than in adults. Vitamin D deficiency may lead to hypophosphatemia by decreasing intestinal phosphate absorption. Phosphate-binding antacids are used in chronic renal insufficiency and in hypoparathyroidism for the control of hyperphosphatemia, and their use may lead to hypophosphatemia. Severe vomiting and a variety of malabsorptive disorders may also lead to hypophosphatemia.

Chronic alcoholism and alcohol withdrawal are among the most common causes of severe hypophosphatemia [78]. The mechanisms involved have not been extensively studied, but it likely results from a variety of factors. Decreased intestinal absorption of phosphate because of poor dietary intake, vomiting, diarrhea, or routine use of antacids may lead to phosphate depletion. Renal losses of phosphate may result from repeated episodes of ketoacidosis with loss of phosphate from the cells into the urine; in addition, renal phosphate wasting may occur as a result of tubular dysfunction associated with alcohol. Intracellular shifts of phosphate secondary to glucose infusions or respiratory alkalosis may also contribute to hypophosphatemia in these patients.

– *Intracellular shifts of phosphate*

Inorganic phosphate is required for the synthesis of a variety of organic compounds. With stimulation of metabolic pathways, phosphate moves from the extracellular pool into the intracellular space, resulting in hypophosphatemia. One of the common causes of hypophosphatemia in the hospital setting is respiratory alkalosis due to the hyperventilation induced by a variety of factors, including pain, sepsis, depression, and alcohol withdrawal. The rise in intracellular pH in this setting results in activation of glycolysis, which increases the utilization of inorganic phosphate. Hypophosphatemia in hospitalized patients is also commonly caused by the intravenous administration of carbohydrate, usually in the form of glucose. Glucose administration may cause hypophosphatemia by increasing insulin release, which promotes phosphate uptake by the cell, and by the enhanced incorporation of phosphate into compounds involved in the glycoly-

tic pathway. The hypophosphatemia induced by glucose administration may be severe in patients with starvation. In diabetics, the decrease in serum phosphate following glucose administration is usually mild because of impaired insulin release. Fructose may cause a more severe hypophosphatemia than glucose because of its unregulated uptake by the liver [50]. The nutritional recovery syndrome occurs during the rapid refeeding of patients with starvation, and it is associated with hypophosphatemia, hypokalemia, and hypomagnesemia. Transient hypophosphatemia may occur during recovery from hypothermia because of the associated stimulation of glycolysis with rewarming. The hungry bone syndrome may occur following parathyroidectomy and is characterized by hypocalcemia and hypophosphatemia due to accelerated bone mineralization [79].

– *Increased renal excretion of phosphate*
Hyperparathyroidism causes hypophosphatemia by decreasing renal tubular reabsorption of phosphorus, as discussed earlier. Hypophosphatemia may accompany malignant neoplasms [80]. PTHrP may be produced by certain tumors and act via the PTH/PTHrP receptor in the kidney to decrease phosphate reabsorption. Some tumors of mesenchymal origin may be associated with hypophosphatemia, low levels of calcitriol and osteomalacia. These patients have normal levels of PTH and PTHrP and markedly reduced renal phosphate transport. Calcitriol administration may not improve the phosphate transport defect. Tumors associated with this syndrome are thought to secrete a phosphaturic substance that acts directly in the renal tubular cells by inhibiting sodium-dependent phosphate uptake [66].

Disorders of vitamin D metabolism, such as vitamin D deficiency and vitamin D-dependent and vitamin D-resistant rickets, are associated with decreased renal reabsorption of phosphate and hypophosphatemia. Decreased intestinal phosphate absorption may also contribute to the hypophosphatemia in these disorders. In vitamin D deficiency, the decreased tubular reabsorption of phosphate is mediated by the high levels of PTH from hypocalcemia. Vitamin D-resistant rickets or familial X-linked hypophosphatemic rickets (XLH) is similar to oncogenic osteomalacia with regard to the pathophysiologic process of hypophosphatemia. The genetic abnormality in XLH is based on mutations in the PEX gene (*p*hosphate-regulating gene with homologies to *e*ndopeptidases on the *X*-chromosome) [81]. The abnormal endopeptidase activity of the mutated gene product has been postulated to result in impaired degradation of a phosphaturic factor.

Vitamin D-dependent rickets (VDDR), also a familial disorder associated with a tubular defect in phosphate reabsorption, has been classified into types I and II. Type I VDDR is an autosomal recessive disorder that presents in early childhood with hypophosphatemia, hypocalcemia, rickets, low serum levels of calcitriol, and elevated serum levels of 25(OH)D. Patients respond to therapy with small doses of calcitriol, suggesting abnormal production of calcitriol by the kidney as the primary abnormality. Indeed, the human 1-α-hydroxylase gene has been recently found to map to the previously identified disease locus for type I VDDR, which strongly suggests that mutations of this gene are the basis for this disorder [82]. Type II VDDR is actually a form of vitamin D resistance, and it is associated with end-organ resistance to calcitriol because of mutations in the gene encoding the vitamin D receptor [83, 84]. Clinically, type

II VDDR is indistinguishable from type I VDDR except that calcitriol levels are elevated, and treatment with calcitriol is ineffective.

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is also characterized by decreased renal reabsorption of phosphate and is thought to represent a primary defect in tubular phosphate reabsorption. Idiopathic hypercalciuria may potentially represent a milder form of this disorder [85]. X-linked recessive nephrolithiasis with renal failure is a form of hereditary renal disease associated with renal phosphate wasting [86] and may represent a generalized defect in proximal tubular function. The Fanconi syndrome is a generalized impairment in proximal tubular function because of either hereditary abnormalities or acquired conditions, such as multiple myeloma. The resultant injury to the proximal tubular epithelium induces urinary losses of solutes normally reabsorbed in this nephron segment such as phosphorus, glucose, amino acids, bicarbonate and uric acid. Successful kidney transplantation may be associated with hypophosphatemia that is mostly due to a tubular phosphate leak secondary to persistent hyperparathyroidism. However, a variety of other factors may also contribute to post-transplant hypophosphatemia, including glucocorticoids, chronic volume expansion, and diuretics as well as the shift of phosphate and calcium into bone associated with the correction of hyperparathyroidism.

Metabolic acidosis decreases renal tubular reabsorption of phosphate and may cause hypophosphatemia. In addition, acidosis results in shifts of phosphate from the intracellular pool because of the breakdown of intracellular organic compounds. The released phosphate is excreted in the urine and may contribute to phosphate depletion. In diabetic ketoacidosis, the catabolic effects of insulin deficiency also contribute to the shift of phosphate into the extracellular fluid, thus worsening the phosphaturia. A variety of drugs such as thiazide diuretics and high doses of estrogen can induce renal phosphate wasting and cause hypophosphatemia.

Management of Hypophosphatemia

Patients with moderate hypophosphatemia (serum phosphorus between 1 and 2.5 mg/dL) who do not have a history of GI or renal phosphate losses rarely require phosphate replacement; rather, the treatment is aimed at the underlying cause. For example, in patients with uncomplicated diabetic ketoacidosis, the hypophosphatemia usually corrects spontaneously with normal dietary intake, and it may not be necessary to treat the hypophosphatemia per se. Likewise, patients with hypophosphatemia due to vitamin D deficiency respond to therapy with vitamin D supplementation. Phosphate supplementation, either orally or intravenously, is indicated in patients who are symptomatic; however, the latter should be reserved for patients with life-threatening complications or for those who are unable to tolerate oral feeding.

Magnesium

Normal Magnesium Homeostasis

Magnesium is the second most abundant intracellular cation. Fifty to 60% of total body magnesium is in bone, with the remainder in the soft tissues [87]. Intracellular magnesium

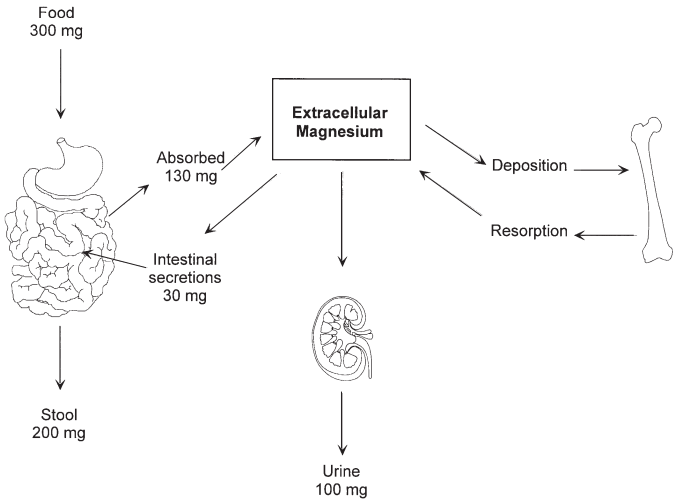

Figure 5. Normal magnesium homeostasis.

concentration is 8 – 10 mM and is mostly bound to ATP and other nucleotides and enzymes. Free magnesium concentrations are approximately 10% of total. Less than 1% of body magnesium is in the extracellular fluid and therefore, serum magnesium, like serum potassium, is not a very sensitive indicator of body stores. Serum magnesium is in 3 fractions: ionized (60%), complexed, usually with citrate or phosphate (15%) and bound to protein, mainly albumin (25%). Normal serum magnesium concentration is 1.7 – 2.3 mg/dL, of which 75% is ultrafiltrable.

Intestinal Absorption of Magnesium

The average daily intake from a variety of foods is 300 mg. As illustrated in Figure 5, approximately one-third of the ingested magnesium is absorbed, principally in the small bowel, by a saturable as well as by a passive diffusional process [88]. Some magnesium is also secreted into the intestine (approximately 30 mg). Thus, net absorption is about 100 mg. Little evidence exists for regulation of magnesium absorption in the intestine.

Renal Handling of Magnesium

In contrast to most other cations, the proximal tubule is not the major site of reabsorption of magnesium, and only 15 – 20% of filtered magnesium (ionized plus complexed) is absorbed in this segment. The major site of magnesium reabsorption is the thick ascending loop of Henle, in which 60 – 70% of the filtered magnesium is reabsorbed [89 – 91]. A large portion of the reabsorption of magnesium in this segment is by the paracellular route and is driven by the lumen positive potential resulting from the activity of the Na-K-2Cl transporter. There is also evidence that magnesium reabsorption in this segment can be regulated by hormones, e.g. PTH, suggesting additional transcellular absorption mechanisms [92].

However, hormonal effects could also be explained by alterations in sodium chloride reabsorption. Little is known about the mechanisms of magnesium reabsorption in the distal nephron, but it is believed to occur by entry through luminal magnesium channels and exit via a Na/Mg exchanger [91, 93].

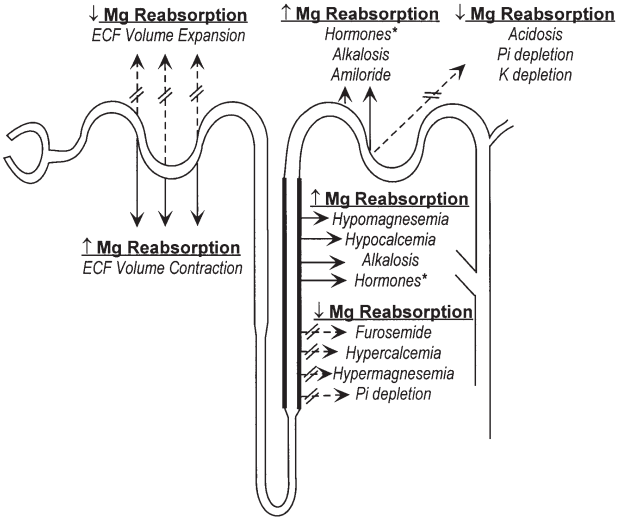

Figure 6. Factors regulating magnesium excretion
*Hormones: Parathyroid hormone, Calcitonin, Glucagon, Vasopressin.

Regulation of Magnesium Excretion

Factors regulating magnesium excretion are illustrated in Figure 6. Alteration in magnesium excretion is mainly a consequence of changes in the level of plasma magnesium, which is a potent regulator of magnesium reabsorption in the thick ascending limb [94]. Thus, hypermagnesemia decreases magnesium reabsorption, and hypomagnesemia is associated with a marked decrease in magnesium excretion. The recently described calcium-sensing receptor, which may also bind magnesium, may be involved in this regulation of magnesium reabsorption [2, 4, 95, 96]. Hypercalcemia, which inhibits magnesium reabsorption, may also affect this mechanism. Magnesium reabsorption is stimulated by PTH in this segment. Phosphate depletion [97] and systemic acidosis [98] are associated with marked hypermagnesuria. Alcohol administration, volume expansion, and glycosuria also increase magnesium excretion [99, 100]. Diuretics, both distally acting thiazides and the loop diuretics, increase magnesium excretion.

Table 5. Causes of Hypermagnesemia

Decreased renal excretion	
	Acute Renal Failure
	Chronic Renal Failure
Increased entrance to extracellular fluid	
	Magnesium-containing laxatives
	Magnesium-containing enemas
	Magnesium-containing IV fluids
	Parenteral magnesium, e.g. treatment of eclampsia

Hypermagnesemia

In normal subjects, ingested magnesium is readily excreted by the kidneys and hypermagnesemia is uncommon. Infused magnesium loads are excreted within 48 hours. Causes of hypermagnesemia are listed in Table 5. Hypermagnesemia occurs in the presence of renal failure or after large loads given by infusion or by enema. In renal failure, serum magnesium remains in the normal range until renal failure is advanced, and even

then, only modest elevations occur [101]. Severe hypermagnesemia only occurs following the injudicious ingestion or administration of magnesium-containing antacids or enemas. These should be avoided in patients with advanced renal failure. Magnesium infusions may be administered for eclampsia and usually achieve a blood concentration of 6 – 8 mg/dL. Other causes of elevations of serum magnesium are uncommon and mild.

Clinical Consequences of Hypermagnesemia

The principal manifestation of hypermagnesemia is neuromuscular toxicity shown first by decreases in reflexes (4 – 6 mg/dL) followed by somnolence and muscular paralysis, including respiratory paralysis, as magnesium rises to higher levels [102]. Hypermagnesemia acts as a calcium channel blocker in the heart and as intracellular magnesium increases, potassium channels also become blocked [103]. These effects lead to bradycardia and hypotension with abnormal ECG changes of prolonged PR interval, widened QRS, and an increase in QT interval. Complete heart block may occur, and cardiac arrest may occur at magnesium concentrations > 15 mg/dL. Elevations in magnesium can also decrease the secretion of PTH, and thus hypocalcemia may occur, but is usually transient and mild. A variety of non-specific symptoms may also occur such as nausea, vomiting, and flushing.

Hypomagnesemia

Hypomagnesemia is common in hospitalized patients (10%) and may reach 50% in patients in intensive care units [104 – 106]. The main factors involved in this setting are poor nutrition, hypoalbuminemia, and aminoglycosides. The causes of hypomagnesemia are listed in Table 6. These causes should serve to raise the awareness of potential problems in these settings and prompt the measurement of serum magnesium [107]. Decreased intake may be the cause of hypomagnesemia in protein-calorie malnutrition and in patients who have received intravenous fluids for prolonged periods. Decreases in intestinal absorption may occur with malabsorption syndromes, either from nontropical sprue or Crohn's disease or following extensive bowel resections. Biliary fistulae and prolonged nasogastric suction may also cause magnesium

Table 6. Causes of Hypomagnesemia

Decreased intake	
	Protein calorie malnutrition
	Starvation
	Prolonged intravenous fluids
Decreased intestinal absorption	
	Malabsorption syndromes
	Intestinal resection
Excess urinary losses	
	Diuretics
	Post-ATN
	Alcohol administration
	Primary aldosteronism
	Drugs : aminoglycosides, cyclosporine, cisplatin
	Phosphate depletion
	Prolonged glycosuria
	Inherited disorders of tubular transport: Bartter and Gitelman syndromes
Excess losses of body fluids	
	Prolonged NG suction
	Biliary fistula
	Severe diarrheal states
Other	
	Pancreatitis
	Blood transfusions
	Hungry bone syndrome

depletion. Urinary losses also account for a number of cases of magnesium deficiency. Diuretic therapy is often associated with hypomagnesemia, and increased renal magnesium losses occur in glycosuric states such as diabetic ketoacidosis, primary hyperaldosteronism, volume expansion, following acute tubular necrosis (ATN), and from a variety of drugs including aminoglycosides, cyclosporine, and cisplatin. Some cases of Bartter syndrome and all cases of Gitelman syndrome are hypomagnesemic [108 – 110]. Phosphate depletion is associated with magnesuria although the mechanism is not well understood. An additional category which should be considered is that of redistribution of magnesium within the body such as might occur after parathyroidectomy, i.e. hungry bone syndrome [20, 111] or in association with acute pancreatitis [112]. The renal losses are most commonly due to diuretic therapy and generally are mild because the volume contraction results in increased proximal reabsorption.

Clinical Consequences of Hypomagnesemia

Hypomagnesemia is often associated with other electrolyte abnormalities so that it may be difficult to ascribe the particular symptom to the low levels of magnesium. However, typical signs of magnesium deficiency are tetany and positive Chvostek and Trousseau signs as a manifestation of neuromuscular irritability [113]. Tetany may occur without frank hypocalcemia, but hypocalcemia is commonly present in severe magnesium deficiency. Abnormal cardiac function may be manifested by wide QRS with peaking of T waves and increased ventricular arrythmias. Hypokalemia is associated with hypomagnesemia in almost 50% of cases, possibly indicating that the causes for decreases in these electrolytes are similar. However, hypokalemia may be refractory to potassium supplementation until the magnesium deficit is corrected [114]. Severe hypocalcemia may coexist, and this is related to a profound defect in PTH secretion [115]. Magnesium replenishment results in a rapid increase in the release of PTH within minutes of administration [116]. The hypocalcemia of magnesium depletion is also due to a skeletal resistance to the actions of PTH [117].

Diagnosis and Therapy of Hypomagnesemia

Since measurement of magnesium is not routine, magnesium deficiency can often go unrecognized. Magnesium should be measured in the clinical circumstances mentioned above, and if low, should be replenished and the cause identified and corrected. Distinction between GI and renal losses can be made by measurement of 24-hour urine magnesium values or the fractional excretion of magnesium, since the normal renal response to magnesium deficiency is to increase magnesium reabsorption and to decrease magnesium excretion to low levels. Prophylactic administration of magnesium may be considered in certain clinical circumstances if renal function is normal. Potassium-sparing diuretics may be considered in cases of renal magnesium wasting. Replacement therapy should be by the oral route if possible, but parenteral administration can be utilized if the manifestations of hypomagnesemia are severe or if oral administration is not possible or limited because of the diarrhea induced by oral supplements.

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