CHAPTER

73 Disorders of Phosphorus, Calcium, and Magnesium Metabolism

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PHOSPHORUS

Phosphorus is a common anion ubiquitously distributed throughout the body. Approximately 80% to 85% of the phosphorus is present in the skeleton. The rest is widely distributed in the form of organic phosphate compounds that play fundamental roles in several aspects of cellular metabolism. The energy required for many cellular reactions including biosynthesis derives from hydrolysis of adenosine triphosphate (ATP). Organic phosphates are important components of cell membrane phospholipids. In the extracellular fluid (ECF), phosphorus is present predominantly in the inorganic form (Pi). The physiologic concentration of serum phosphorus ranges from 2.5 to 4.5 mg/dL (0.9 to 1.45 mmol/L) in adults.[373] In serum, phosphorus exists mainly as the free ion, and only a small fraction (less than 15%) is protein bound.[274,683] There is a diurnal variation in serum phosphorus of 0.6 to 1.0 mg/dL, with the nadir occurring between 8 AM and 11 AM.

Phosphorus Balance and Gastrointestinal Absorption

Approximately 1 g of phosphorus is ingested daily in an average diet in the United States. About 300 mg is excreted in the stool, and 700 mg is absorbed (Fig. 73.1). Most of the phosphorus is absorbed in the duodenum and jejunum with minimal absorption occurring in the ileum.[204] Phosphorus transport in proximal segments of the small intestine appears to involve both passive and active components and to be under the influence of vitamin D. The movement of phosphorus from the intestinal lumen to the blood requires (1) transport across the luminal brush-border membrane of the intestine; (2) transport through the cytoplasm; and (3) transport across the basolateral plasma membrane of the epithelium. The rate-limiting step and the main driving force of absorption is the luminal membrane step.[373]

Intestinal Epithelial Luminal Membrane Transport

The mechanism of transport across the intestinal brush border epithelial membrane involves a sodium–phosphate (NaPi) cotransport system, NaPi-IIb.[265] The NaPi cotransporters are a secondary active form of ion transport using the energy of the Na gradient from outside to inside the cell to move phosphate ion uphill against an electrochemical gradient (Fig. 73.2).

The intestinal NaPi-IIb transporter is upregulated by a low phosphate diet and 1,25-dihydroxyvitamin D3.[258,314] Although low phosphate diets upregulate1,25-dihydroxyvitamin D3, studies in vitamin D–receptor (VDR) null mice indicate that the intestinal NaPi cotransport adaptation to a low phosphate diet occurs independent of vitamin D.[585]

Intestinal NaPi cotransport activity and NaPi-IIb protein is also regulated by several other factors—including the aging process,[722] glucocorticoids,[26] epidermal growth factor (EGF),[723] and liver X receptor (LXR)[106]—that decrease intestinal NaPi transport, and estrogen[724] and metabolic acidosis[638] that increase intestinal NaPi transport.

Studies of phosphorus accumulation by rat intestinal brush-border vesicles have demonstrated that it is affected by the transmembrane potential, indicating that like the renal type IIa cotransporter, NaPi-IIa, the intestinal type IIb cotransporter, NaPi-IIb, is electrogenic.[265] The $K_m(P_i)$ of NaPi-IIb is approximately 50 μm, similar to the renal transport protein. In contrast to the renal NaPi-IIa isoform, the intestinal NaPi-IIb cotransporter is less dependent on the pH level.

Transcellular Movement of Phosphorus

The second component of transcellular intestinal phosphorus transport involves the movement of phosphorus from the luminal to the basolateral membrane. Although little is known about the cellular events that mediate this transcellular process, evidence suggests a role for the microtubular microfilament system of intestinal cells.[204] Microfilaments in the cell may be important in conveying phosphorus from the brush-border membrane to the basolateral membrane and may be involved in the extrusion of phosphorus at the basolateral membrane from the epithelial cell.

Phosphate Exit at Basolateral Membrane

Little is known about the mechanisms of phosphorus extrusion at the basolateral membrane of intestinal epithelial cells.

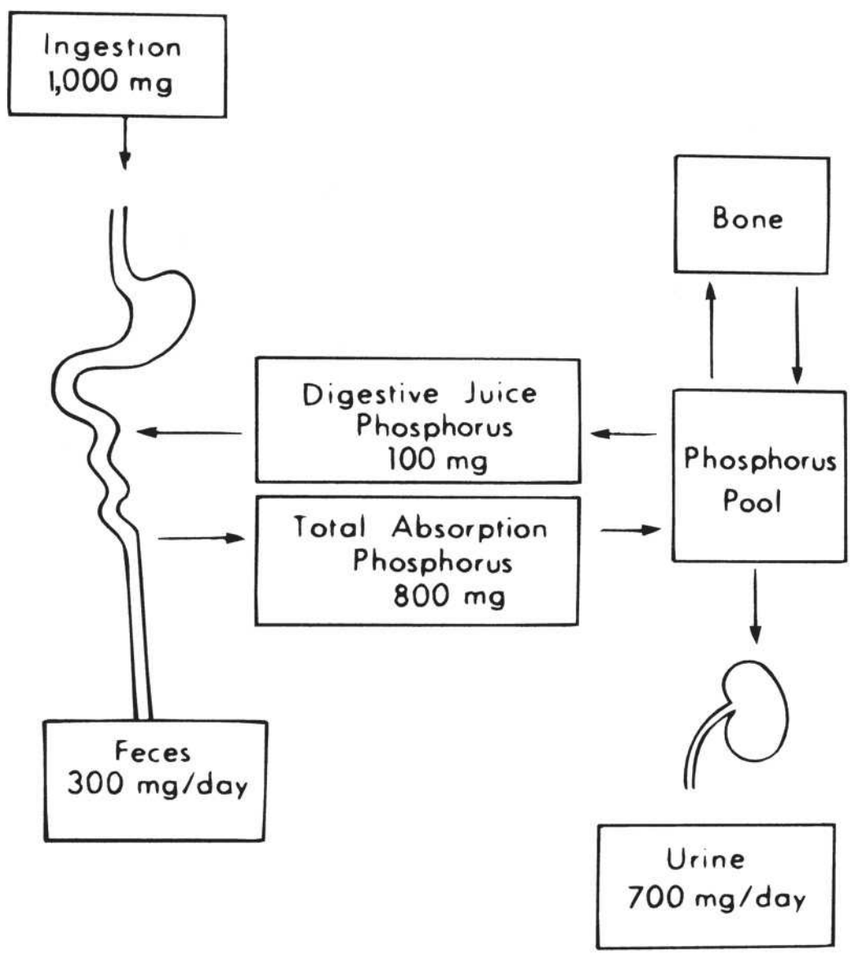


FIGURE 73.1 Summary of phosphorus metabolism in humans. Approximately 1 g of phosphorus is ingested daily, of which 300 mg is excreted in the stool and 700 mg in the urine. The gastrointestinal tract, bone, and kidney are the major organs involved in phosphorus homeostasis.

The electrochemical gradient for phosphorus favors movement from the intracellular to the extracellular compartment because the interior of the cell is electrically negative compared with the basolateral external surface. Therefore, the presumption has been that the exit of phosphorus across the basolateral membrane represents a mode of passive transport.[321]

Renal Excretion of Phosphorus, Reabsorption

Most of the inorganic phosphorus in serum (90% to 95%) is ultrafiltrable at the level of the glomerulus. At physiologic levels of serum phosphorus, approximately 7 g of phosphorus is filtered daily by the kidney, of which 80% to 90% is reabsorbed by the renal tubules and the remainder is excreted in the urine (approximately 700 mg on a 1-g phosphorus diet)

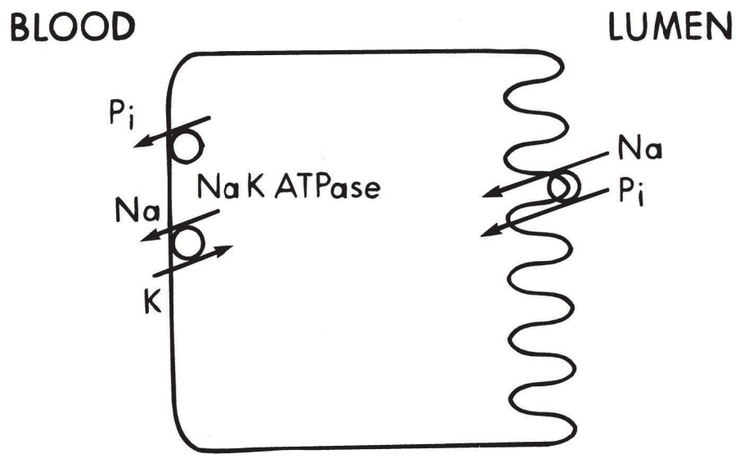


FIGURE 73.2 The apical membrane sodium–inorganic phosphate (Pi) cotransport proteins utilize the electrochemical driving force for sodium to move Pi into the cell. The electrochemical sodium gradient is maintained by active sodium extrusion across the basolateral membrane through the action of Na^+-K^+-ATPase.

equal to intestinal absorption.[332] As a result, adults are generally in balance between phosphorus intake and excretion (Fig. 73.1). Micropuncture studies have demonstrated that 60% to 70% of the filtered phosphorus is reabsorbed in the proximal tubule. However, there is also evidence that a significant amount of filtered phosphorus is reabsorbed in distal segments of the nephron.[502] When serum phosphorus levels increase and the filtered load of phosphorus increases, the capacity to reabsorb phosphorus also increases. However, a maximum rate of transport (Tm) for phosphorus reabsorption is obtained usually at serum phosphorus concentrations of 6 mg per dL. There is a direct correlation between Tm phosphorus values and glomerular filtration rate (GFR) even when the GFR is varied over a broad range. Micropuncture studies suggest two different mechanisms responsible for phosphorus reabsorption in the proximal tubule. In the first third of the proximal tubule, in which only 10% to 15% of the filtered sodium and fluid is reabsorbed, the ratio of tubular fluid (TF) phosphorus to plasma ultrafiltrable (UF) phosphorus falls to values of approximately 0.6. This indicates that the first third of the proximal tubule accounts for approximately 50% of the total amount of phosphorus reabsorbed in this segment of the nephron. In the last two thirds of the proximal tubule, the reabsorption of phosphorus parallels the movement of salt and water. In the remaining 70% of the pars convoluta, the TF:UF phosphorous ratio remains at a value of 0.6 to 0.7, whereas fluid reabsorption increases to approximately 60% to 70% of the filtered load. Thus, in the last two thirds of proximal tubule, the TF:UF phosphorus reabsorption ratio is directly proportional to sodium and fluid reabsorption. A significant amount of phosphorus, perhaps on the order of 20% to 30%, is reabsorbed beyond the portion of the proximal tubule that is accessible to micropuncture. There is little phosphorus transport within the loop of Henle, with most transport distal to micropuncture accessibility occurring in the distal convoluted tubule. In this location, Pastoriza-Munoz et al.[502] found that approximately 15% of filtered phosphorus is reabsorbed under baseline conditions in animals subjected to parathyroidectomy, but that the value falls to about 6% after administration of large doses of parathyroid hormone (PTH). The collecting duct is a potential site for distal nephron reabsorption of phosphorus.[115,508,592] Transport in this nephron segment may explain the discrepancy between the amount of phosphorus delivered to the late distal tubule in micropuncture studies and the considerably smaller amount of phosphorus that appears in the final urine of the same kidney. Phosphorus transport in the cortical collecting tubule is independent of regulation by PTH. This is in agreement with the absence of PTH-dependent adenylate cyclase in the cortical collecting tubule.[115]

Comparison of Superficial and Deep Nephron Transport

The contribution of superficial nephrons and deep nephrons of the kidney to phosphorus homeostasis differs.

Nephron heterogeneity in phosphorus handling has been evaluated under a number of conditions by puncture of the papillary tip and the superficial early distal tubule, with the recorded fractional delivery representing deep and superficial nephron function, respectively. Microinjection of phosphorus tracer into thin ascending and descending limbs of loops of Henle reveals that only 80% of phosphorus was recovered in the urine, whereas 88% to 100% of phosphorus was recovered when the tracer was injected into the late superficial distal tubule. It was concluded that a significant amount of phosphorus must be reabsorbed by juxtamedullary distal tubules or by segments connecting the juxtamedullary distal tubules to the collecting ducts to account for the discrepancy between the results of superficial nephron injection and juxtamedullary nephron injections. These data support an increased reabsorptive capacity for phosphorus in deep as opposed to superficial nephrons and increased responsiveness to body Pi requirements.[253,254]

In summary, phosphorus transport occurs in the distal nephron, particularly in the distal convoluted tubule and cortical collecting tubular system. This transport may be considerable under certain experimental conditions, but the importance of the terminal nephron system in day-to-day phosphorus homeostasis remains to be defined. It is also evident from data obtained from various micropuncture and microinjection studies that juxtamedullary and superficial nephrons have different capacities for phosphorus transport. The increased responsiveness of the deep nephrons to phosphorus intake suggests a key regulatory role for this system in phosphorus homeostasis.

Cellular Mechanisms of Phosphate Reabsorption in the Kidney

The apical membrane of renal tubular cells is the initial barrier across which phosphorus and other solutes present in the tubular fluid must pass to be transported into the peritubular capillary network. Because the electrical charge of the cell interior is negative to the exterior, and phosphorus concentrations are higher in the cytosol, phosphorus must move against an electrochemical gradient into the cell interior, whereas at the antiluminal membrane, the transport of phosphorus into the peritubular capillary is favored by the high intracellular phosphorus concentration and the electronegativity of the cell interior. Studies with apical membrane vesicles have demonstrated cotransport of Na^+ with phosphate across the brush-border membrane, whereas the transport of phosphorus across the basolateral membrane is independent of that of Na^+.[272] The apical membrane Na^+-phosphate cotransport protein (NaPi-IIa) energizes the uphill transport of phosphate across the brush-border membrane (BBM) by the movement of Na^+ down its electrochemical gradient. The latter gradient is established and maintained by active extrusion of Na^+ across the basolateral cell membrane into the peritubular capillary through the action of Na^+-K^+-ATPase (Fig. 73.2).[571]

Three families of NaPi cotransport proteins of the proximal tubule (types I, II, and III) have been cloned.[414,472,473,636,661,709] The DNA clones encode 80- to 95-kd proteins that reconstitute Na^+-dependent concentrative, or "uphill," transport of phosphate.[203,414,636] The type I cotransporter, Npt1/SLC17, is expressed predominantly in the renal proximal tubule, and it accounts for about 13% of the known NaPi cotransporter mRNA in the mouse kidney.[662] Npt1 is not regulated by dietary Pi, and studies in Npt1-cRNA–injected oocytes revealed that it may function not only as a NaPi cotransporter but also as a chloride and organic anion channel.[103]

The type II cotransporter NaPi-II/SLC34 proteins are similar between several species including humans.[472,473,661] In addition to NaPi-IIa, the predominant isoform in the renal proximal tubule, another isoform, NaPi-IIc, has been discovered.[486,584,586,660] Nephron localization of NaPi-II proteins has been limited to the proximal tubule of superficial and deep nephrons (greatest in the latter, concordant with physiologic studies).[472,473,661] Immunolocalization studies in renal epithelial cells demonstrated apical membrane and subapical membrane vesicle staining,[472,473,661] suggesting that a functional pool of transporters is available for insertion into or retrieval from the BBM itself. This has been postulated to be a major mechanism of Pi transport regulation in response to acute changes in phosphorus, PTH, MEPE, and fibroblast growth factor 23 (FGF23) levels.[33,472,473,609,661] The NaPi-II family is upregulated at message and protein levels by chronic feeding of low-Pi diets[368,403] and downregulated at message and protein levels by PTH[136,368,403] and dietary potassium deficiency.[92]

The type III NaPi cotransporters SLC20 were originally identified as retroviral receptors for gibbon ape leukemia virus (Glvr1) and rat amphotropic virus (Ram1).[317] They are ubiquitously expressed, and they comprise about 1% of the known NaPi cotransporter mRNAs in the mouse kidney.[662] Pit-2 protein is expressed in the apical membrane of the renal proximal tubule and the levels are regulated by dietary Pi,[678] dietary potassium,[92] and LXR.[106]

Studies of phosphorus exit across the basolateral membrane suggest that it is accompanied by the net transfer of a negative charge and occurs down a favorable electrochemical gradient via sodium-independent mechanisms.[582]

Proteins that Interact with the Type IIa and Type IIc Na/Pi Cotransporter Proteins

Several proteins with PDZ domains have been identified that interact with the NaPi-IIa and NaPi-IIc protein and are localized in the BBM or the subapical compartment (Fig. 73.3). PDZ domains are modular protein interaction domains that often occur in scaffolding proteins and bind in a sequence-specific fashion to the C-terminal peptide sequence or at times the internal peptide sequences of target proteins. These domains of approximately 90 amino acids are known by an acronym of the first three PDZ-containing proteins identified including the postsynaptic protein PSD-95/SAP90, the

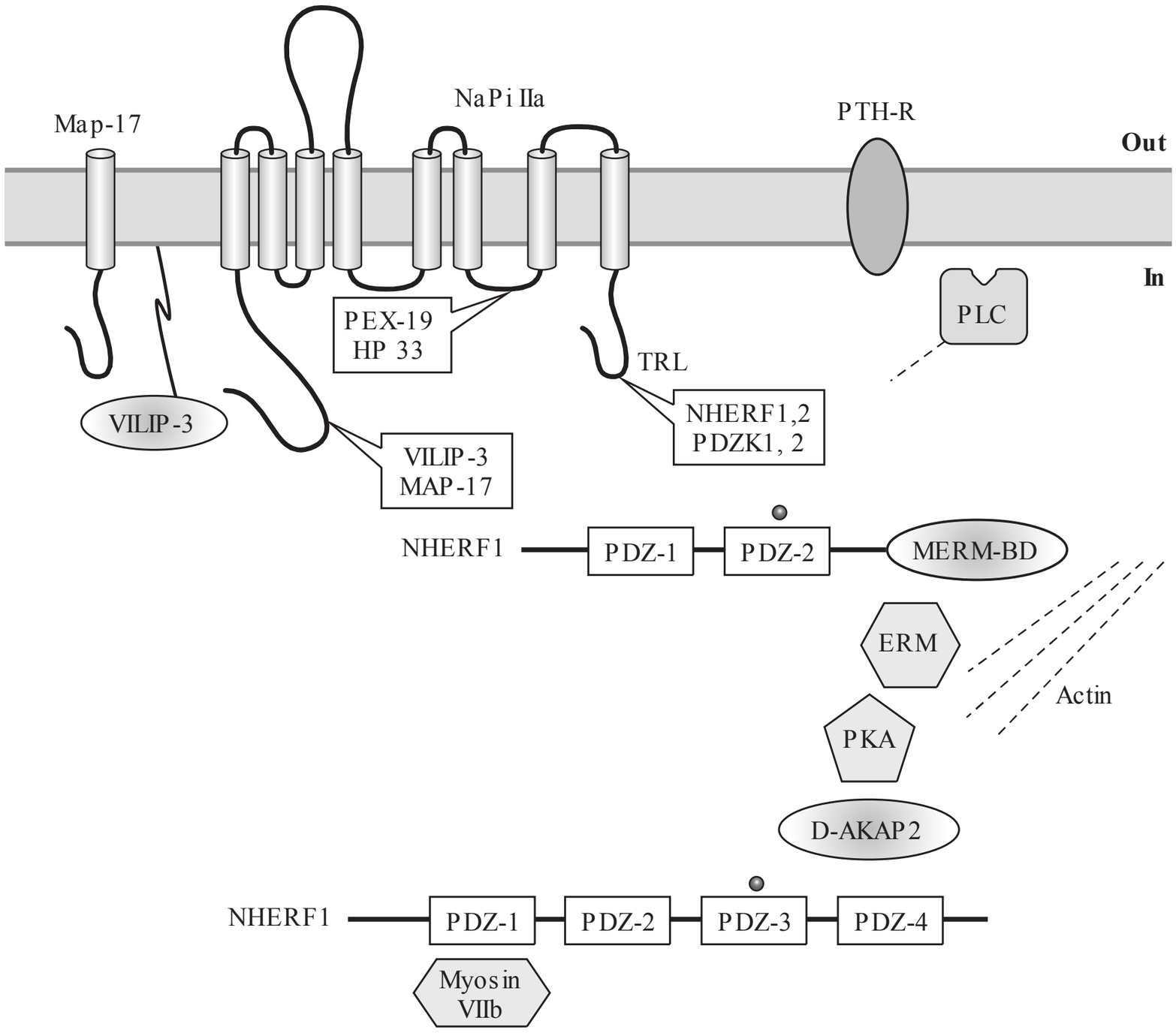


FIGURE 73.3 Interactions of NaPi-IIa with several proteins expressed in the renal proximal tubule. MAP-17 is involved in the apical location of PDZK1 (via PDZ-4) in OK cells. (From Biber J, Gisler SM, Hernando N, et al. PDZ interaction and proximal tubular phosphate reabsorption. *Am J Physiol Renal Physiol.* 2004;287:F871.)

Drosophila septate junction protein Discs-large, and the tight junction protein ZO-1.[255,288,367,596]

PDZ domain containing proteins including NHERF-1, NHERF-2, PDZK1, CAL, and ZO-1 play an important role in: (1) the regulation of the expression and activity of renal proximal tubular BBM transport proteins including NHE-3,[596,697–700] NaPi IIa,[33,359] and NaPi-IIc[219,677] and basolateral membrane transport proteins including Na-K-ATPase[359] and Na-HCO_3 cotransporter (NBC)[696]; (2) the regulation of the expression and activity of cystic fibrosis transmembrane conductance regulator (CFTR), a cAMP-regulated chloride channel and channel regulator[389,477,540,653,686]; (3) parathyroid hormone 1 receptor signaling[417] and endocytic sorting of the β2-adrenergic receptor[107] and platelet-derived growth factor receptor (PDGFR)[313,436]; (4) epithelial cell polarity and formation of tight junctions[64,289]; and (5) maintaining the integrity of the glomerular barrier to proteins through interactions with podocalyxin, negatively charged sialoprotein expressed on the surface of podocytes, the glomerular visceral epithelial cells.[284,285,490,503,504,655]

In addition to their interaction with membrane proteins and receptors, the PDZ domain-containing proteins also interact with the F-actin cytoskeleton through their interactions with the ezrin-radixin-moesin (ERM) proteins (Fig. 73.3).[91,524,633] ERM proteins are typically located peripherally in the membrane and link the cytoplasmic tails of membrane proteins and receptors to the cortical actin cytoskeleton. The ERM proteins play an important role in the formation of microvilli, cell-cell junctions, and membrane ruffles and also participate in signal transduction pathways. The ERM proteins contain an F-actin binding site within their carboxy-terminal 30 residues. In addition, the ERM proteins have FERM (**f**our-point one, **e**zrin, **r**adixin, **m**oesin) domains, which are generally located at or near the amino terminal, and act as multifunctional protein and lipid binding sites. The FERM domain of ezrin interacts strongly with NHERF-1 and NHERF-2. NHERF-1 and NHERF-2 have 2 PDZ domains and have a carboxy-terminal sequence of 30 amino acids that bind ezrin.

Using the molecular approach (yeast two-hybrid) several proteins with PDZ domains that interact with the C terminus of NaPi-IIa have been identified including: (1) NHERF-1/EBP50, (2) NHERF-2/E3KARP, (3) PDZK1/NaPi-Cap1, (4) PDZK2/NaPi-Cap2, and (5) CAL, a CFTR-associated ligand.[60,68,220–222,263,456,516,594]

Different studies suggest that apical expression of NaPi-IIa depends on the presence of NHERF-1. Expression of NaPi-IIa was reduced upon introduction of dominant-negative form of NHERF-1 in OK cells.[220–222,263] The in vivo importance of the

NaPi-IIa interaction with NHERF-1 was also shown in a study where targeted disruption of the mouse NHERF-1 gene was associated with decreased BBM expression and increased intracellular localization of NaPi-IIa resulting in decreased renal phosphate reabsorption and renal phosphate wasting.[595] On the other hand targeted disruption of NHERF-1 did not modulate the BBM expression and localization of NHE3; however, there was impaired regulation of NHE3 in response to PKA.[595]

In contrast to NHERF-1, targeted disruption of the PDZK1 gene failed to modulate the BBM expression of NaPi-IIa.[108,334] NHERF-1, therefore, plays a critical and unique role in the renal proximal tubular apical membrane targeting of NaPi-IIa protein and maintenance of phosphate homeostasis. However targeted disruption of PDZK1 modulates the BBM expression of NaPi-IIc, as compared to NaPi-IIa PDZK1, which has preferential interactions with NaPi-IIc.[219,677]

Recent studies have identified at least three additional proteins that may be important in the regulation of NaPi-IIa targeting and trafficking: (1) the peroxisomal protein PEX 19, a farnesylated protein that confers PTH responsiveness to NaPi-IIa[297]; (2) the calcium binding protein Vilip-3, a myristoleated protein that may be important in calcium dependent regulation of NaPi-IIa[517]; and (3) MAP 17 which may be important for apical expression of PDZK1 (Fig. 73.3).[516]

Factors that Affect the Urinary Excretion of Phosphorus

Of the multiplicity of factors that regulate phosphate transport in the kidney, the most important are dietary phosphate, PTH, and FG23.

Alterations in Dietary Phosphorus Intake

The mechanism by which the kidney modulates phosphorus excretion when dietary phosphorus is reduced or increased continues to be intriguing. Earlier micropuncture studies suggested that the most striking adaptive increase in phosphorus transport occurs in the proximal tubule. Later studies[707] suggested that the entire nephron participates in the reduction of phosphorus excretion during dietary phosphorus deprivation. It has been shown that isolated perfused tubules obtained from rabbits that were fed a normal or low-phosphorus diet differ in their capacity to reabsorb phosphate. In normal animals, the proximal convoluted tubule (PCT) is capable of reabsorbing 7.2 ± 0.8 pmol/mL/min, whereas tubules obtained from phosphorus-deprived animals reabsorb 11.1 ± 1.3 pmol/mL/min. Conversely, animals that are fed a high phosphorus diet show reduced phosphorus reabsorption when the proximal tubules are perfused in vitro (2.7 ± 2.6 pmol/mL/min).

The effect of reduced dietary phosphorus to stimulate renal phosphorus transport is intrinsic to the renal tubular epithelium and occurs at the BBM Na^+-phosphate cotransporter. The adaptation to phosphate supply by the sodium–phosphate cotransporter is biphasic.[61,85,113] Incubation of cells in a low-phosphate medium result in a twofold increase in Na^+-independent phosphate cotransport. The first phase of adaptation is observed rapidly (within 10 minutes) and is characterized by an increase in the V_{max} of the transporter. This initial phase is independent of new protein synthesis.[368,369,403] A slower phase resulting in a doubling of the phosphate transport rate, also through an increase in V_{max}, occurs over several hours and is inhibited by blocking new protein synthesis.[708] The adaptation to acute Pi deprivation occurs independent of de novo transcription and protein synthesis and is mediated by apical insertion of cytoplasmic NaPi-II a transporters by a microtubule dependent mechanism (Fig. 73.4).[402] Secondly, through gene transcription and increased NaPi protein synthesis, additional units are produced and inserted into the brush border. Dietary Pi deprivation also induces the upregulation of NaPi-IIc and Pit-2 in the apical brush border membrane; however, the response of these two transporters is delayed and unlike NaPi-IIa may be dependent on de novo protein synthesis.[677]

Effects of Parathyroid Hormone on Phosphorus Reabsorption by the Kidney

Parathyroidectomy decreases urinary phosphorus excretion, whereas PTH administration increases phosphorus excretion.[57,525] Micropuncture studies indicate that PTH inhibits phosphorus transport in the proximal tubule[9] and in segments of the nephron located beyond the proximal tubule.[502] TF:UF phosphorus ratio reaches a value of 0.6 by the S_2 segment of the proximal tubule and, once achieved, this equilibrium ratio is maintained along the accessible portion of the proximal tubule. Within 6 to 24 hours after parathyroidectomy, the proximal TF:UF phosphorus ratio falls to a value of 0.2 to 0.4, indicating an increase in phosphorus reabsorption.[41,43,707] TF phosphorus falls progressively with continuous fluid absorption along the length of the tubule, so by the end of the proximal tubule, the reabsorption of phosphorus is 70% to 85% of the filtered load, resulting in decreased phosphorus delivery to distal segments of the nephron. In the nonphosphorus-loaded, acutely parathyroidectomized animal, virtually all the distal load of phosphorus is reabsorbed by the distal nephron, reducing urinary phosphorus excretion to very low levels.[333,358] In the phosphorus-loaded animal, the distal reabsorption of phosphorus increases until saturation is approached and urinary phosphorus excretion begins to rise. Acute administration of PTH to phosphorus-loaded parathyroidectomized dogs sharply lowers the distal reabsorption.

Administration of PTH in vivo results in decreased rates of Na^+-dependent phosphorus transport in brush-border membrane vesicles isolated from the kidneys of treated rats.[184,252] Intravenous infusion of dibutyryl cyclic adenosine monophosphate (cAMP) also decreased Na^+-dependent phosphorus uptake in isolated brush-border vesicles, but neither PTH nor dibutyryl cAMP decreased phosphate transport when added directly to membrane vesicles.[184] PTH stimulates two signaling pathways in proximal tubule cells: adenylate cyclase and phospholipase C (PLC), resulting in activation of protein

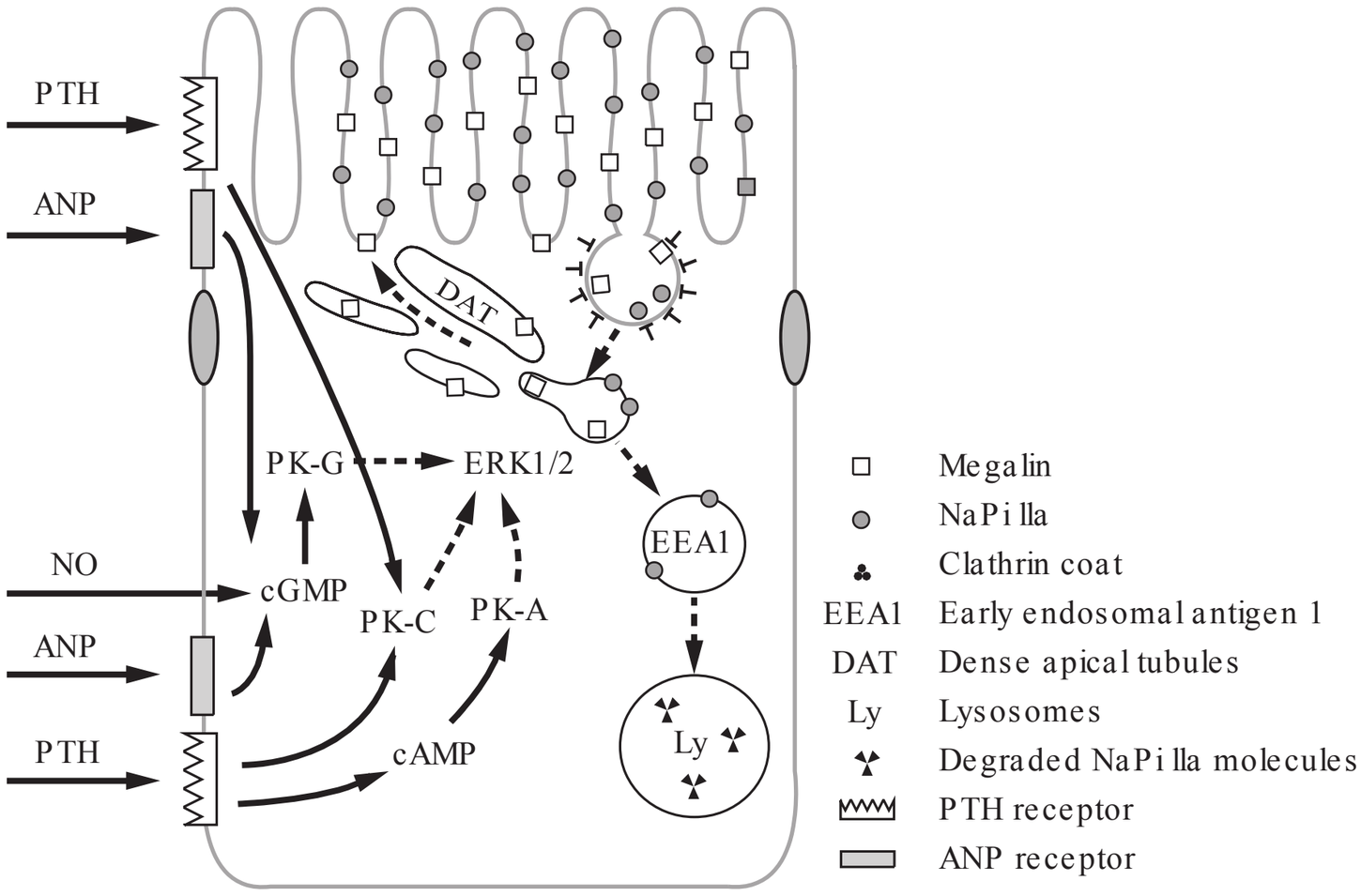


FIGURE 73.4 Mechanisms of NaPi-IIa traffic in the apical membranes of proximal tubular cells. Microvillar NaPi-IIa is retrieved in megalin containing clathrin coated vesicles. NaPi-IIa moves from the vesicles into an endosomal pool marked by EEA-1, whereas megalin is recycled through dense apical tubules back to the microvilli. The endosomal NaPi-IIa is targeted for lysosomal degradation. The process of NaPi-IIa retrieval and lysosomal degradation is stimulated by several factors (parathyroid hormone, atrial natriuretic peptide, nitric oxide) whose mechanisms of signal transduction (PK-A, PK-C, PK-G) merge in activation of ERK1/2 that modulates the process. (From Bacic D, Wagner CA, Hernando N, et al. Novel aspects in regulated expression of the renal type IIa Na/Pi-cotransporter. *Kidney Int*. 2004;66:S5, with permission.)

kinase A (PKA), and protein kinase C (PKC).[174] The first pathway, activation of the adenylate cyclase, differs from that of PKC. Studies in OK cells show that PKA activation by PTH decreases the expression of NaPi-IIa cotransporter likely due to internalization and degradation of the transporter. Binding of PTH to its receptor leads to activation of PLC with the subsequent hydrolysis of phosphatidylinositol 4,5-bisphosphate to inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG). IP_3 generation leads to the release of intracellular calcium stores. DAG activates PKC.[174] In addition to its direct effect on NaPi-IIa, PTH inhibits NaPi transport indirectly by inhibiting the Na^+-K^+-ATPase by decreasing the favorable Na^+ gradient for Pi entry into the cell.[546] Recent studies indicate that the activation of PKA and PKC signaling pathways by PTH also activates mitogen activated protein (MAP) kinase (MAPK) or extracellular receptor kinase (ERK1/2) which also induces inhibition of NaPi transport.[32,360]

Measurement studies of in vivo renal reabsorption of phosphorus and calculations of kinetic parameters of Na^+-dependent phosphorus transport in membrane vesicles isolated from the renal brush-border membranes of normal dogs, parathyroidectomized dogs, dogs fed a low-phosphorus diet, and dogs receiving human growth hormone were performed.[252,281] The latter three groups of dogs had greater baseline values for absolute tubular reabsorption of phosphorus compared with normal dogs. Na^+-dependent phosphate transport in BBM vesicles isolated from kidneys of these dogs was significantly increased compared with transport in brush-border vesicles from kidneys of normal dogs. Administration of PTH decreased significantly the apparent V_{max} for Na^+-dependent phosphorus transport in BBM vesicles isolated from kidneys of each of the four groups of dogs. The apparent K_m (intrinsic binding affinity) for Na^+-dependent phosphorus transport was not significantly changed by experimental maneuvers. Absolute tubular reabsorption of phosphorus measured in vivo was decreased by administration of PTH in each group of dogs with the exception of the dogs fed a low-phosphorus diet.[252,281] Thus, alterations in phosphorus reabsorption measured in vivo were paralleled by alterations in Na^+-dependent phosphorus transport in isolated membrane vesicles, and the administration of PTH in vivo resulted in altered transport characteristics of the isolated BBMs.

The cloning of the NaPi-IIa cotransport proteins did not completely elucidate the mechanisms of PTH action on phosphate transport. Because the phosphaturic effect of PTH can be reproduced by analogs of cAMP, the intracellular mechanism of phosphate transport regulation is thought to involve the cAMP/PKA signal pathway. However, the NaPi-IIa transport proteins are not characterized by a PKA–mediated phosphorylation site.[259] Phosphorylation of BBM proteins in vitro occurs in parallel with inhibition with NaPi-IIa cotransport.[252] Parathyroidectomy of rats causes a twofold to threefold increase in the NaPi-IIa protein content of BBM vesicles.[319] Immunocytochemistry reveals the increase in protein exclusively in apical BBMs of proximal tubules. PTH treatment of parathyroidectomized rats for 2 hours decreased

protein levels and decreased the abundance of NaPi-IIa-specific messenger RNA (mRNA) by 31%.[319] Parathyroidectomy did not affect NaPi-IIa mRNA levels. The effects of PTH were apparent within 2 hours of administration and indicate that PTH regulation of NaPi-IIa is determined by changes in the expression of NaPi-IIa protein in the renal BBMs.[319]

PTH decreases the NaPi-IIa protein content of the apical membrane by a endocytic retrieval pathway which is megalin and myosin VI dependent (Fig. 73.4).[31,67] In megalin intact mice or rats, following treatment with PTH NaPi-IIa is internalized via clathrin-coated pits, and NaPi-IIa is then delivered to early endosomes and eventually to the lysosomes where the protein is degraded. At the present time unlike some of the other proximal tubular transport proteins or receptors, there is no evidence that the NaPi-IIa protein is present at the recycling endosomes.

PTH also regulates the NaPi-IIc protein content of the apical membrane by an endocytic retrieval pathway that is myosin VI–dependent, but the time course is delayed compared to NaPi-IIa.[351]

Fibroblast Growth Factor 23

Through studies of familial hypophosphatemia and tumor induced osteomalacia, a new hormone operating in a systems biology network regulating phosphate homeostasis between the skeleton and the kidney has been discovered (Fig. 73.5).[307,600] The hormone is FGF23, secreted by skeletal osteocytes in response to changes in bone formation and serum phosphorus.[487] The physiology is that the osteocyte monitors deposition of phosphorus into the skeletal reservoir and the saturation of the exchangeable phosphorus pool. When Pi levels increase within the pool due to decreased exit into the skeleton (bone formation) or due to increased plasma phosphorus, osteocytes secrete FGF23, which acts on the renal proximal tubule to decrease reabsorption and increase phosphorus excretion.[279,604]

FGF23 actions at the proximal tubule (PCT) have not been studied as extensively as the actions of PTH, which were described above. Studies indicate that FGF23 acts to decrease expression of NaPi-IIa and NaPi-IIc in the PCT.[209,604] The actions of FGF23 on the PCT are mediated through binding to a FGF receptor—predominantly FGFR1(IIIc) and a coreceptor, Klotho.[673] Signal transduction is stimulated through phosphorylation of extracellular signal-regulated kinase (ERK) and the immediate early response gene, early growth response-1 (Erg-1), a zinc finger transcription factor.[212,673] A matter of current uncertainty is related to KLOTHO expression which is mainly in the renal distal tubule whereas its signaling function is in the PCT. Recent studies have shown that it is expressed in the PCT which would resolve this issue (M. Kuro-o, personal communication).

Besides inhibiting PCT renal Pi transport, FGF23 signaling inhibits PCT CYP27B1, the 25-OH cholecalciferol 1α hydroxylase, and activates 24-OH hydroxylase (CYP24R1) resulting in decreased production and increased catabolism of calcitriol.[600] In addition, activation of 24-OH hydroxylase results in the high prevalence of vitamin D deficiency associated with elevations of FGF23 levels, especially in chronic kidney disease (CKD). Calcitriol increases FGF23, closing the feedback loop in the system (Fig. 73.5).

Vitamin D

Controversy still surrounds the regulatory role of vitamin D in renal phosphorus handling. Several studies have demonstrated that the chronic administration of vitamin D to parathyroidectomized animals is phosphaturic.[75,467,647] Conversely, other investigators reported that vitamin D acutely stimulates proximal tubular phosphorus transport in both

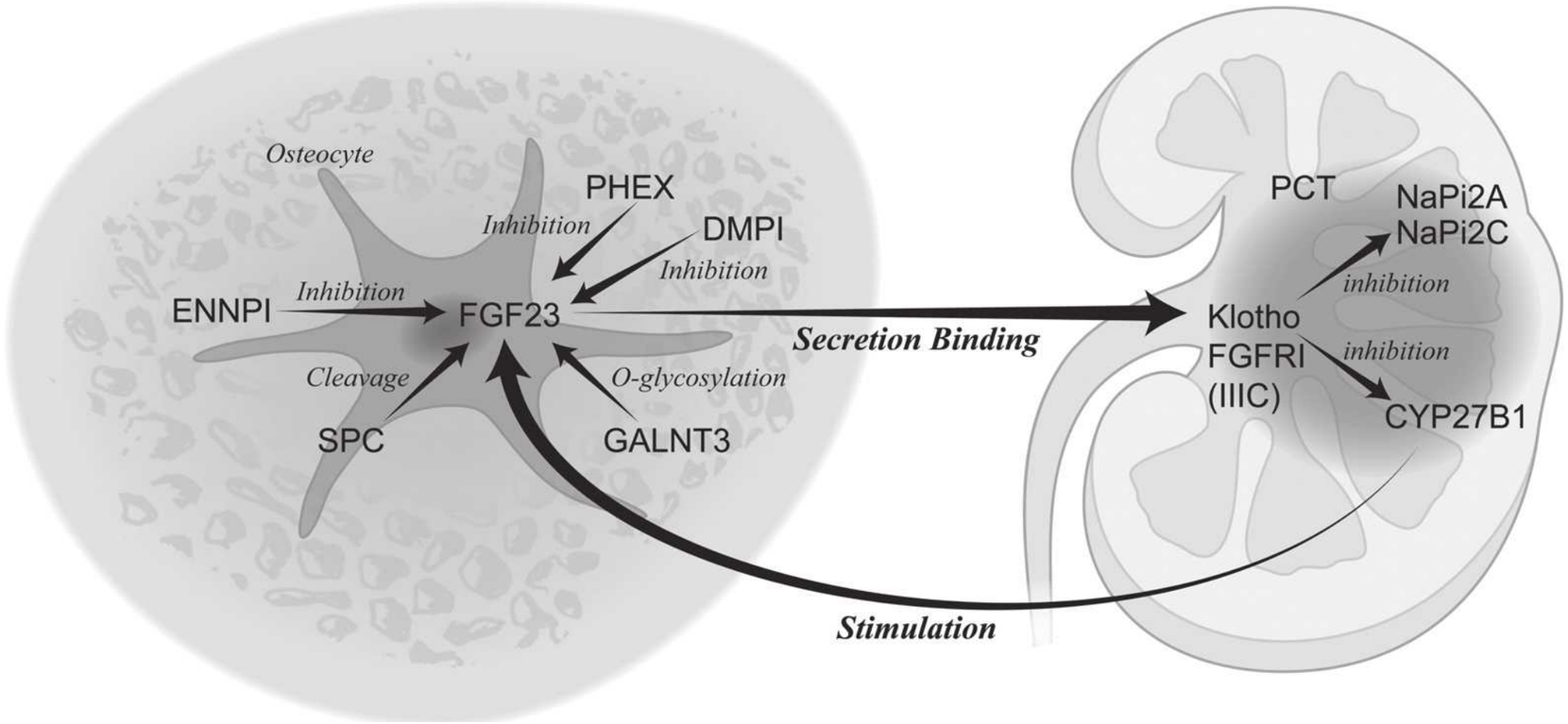


FIGURE 73.5 The skeletal–kidney endocrine axis: regulation of Pi in the exchangeable pool. FGF23 is a hormone secreted by the osteocyte to regulate proximal tubular cell Pi transport and calcitriol production. Multiple mechanisms of increased FGF23 levels cause hypophosphatemic rickets. Calcitriol stimulates FGF23 to maintain Pi levels in response to stimulation of intestinal absorption. Function of various proteins in the endocrine axis and the genetic diseases they cause are listed in Table 73.2.

parathyroidectomized and vitamin D–depleted rats.[211] A unifying interpretation of these studies was hampered by the fact that the dosages of vitamin D administered and the status of the serum calcium, phosphorus, and PTH varied considerably from study to study.

Liang et al.[384] administered 1,25-dihydroxycholecalciferol to vitamin D–deficient chicks and subsequently examined the transport characteristics of isolated renal tubule cells. Three hours after the in vivo administration of vitamin D, phosphorus uptake by the cells was significantly increased, whereas 17 hours after the administration of vitamin D, phosphorus uptake was reduced. The serum phosphorus concentration, however, was significantly increased at 17 hours after administration, and administration of phosphorus to vitamin D–depleted animals so their serum phosphorus levels were comparable to those of the 17-hour vitamin D–replenished group resulted in a similar decrease in phosphorus uptake.[384] In response to in vitro preincubation with as little as 0.01 pm of 1,25-dihydroxycholecalciferol, renal cells isolated from vitamin D–deficient chicks demonstrated a specific increase in sodium-dependent phosphorus uptake, which was blocked by pretreatment with actinomycin D. The stimulatory effect was relatively specific for 1,25-dihydroxycholecalciferol, and kinetic analysis indicated that the V_{max} of the phosphorus transport system was increased, whereas the affinity of the system for phosphorus was unaffected.[384]

Kurnik and Hruska[346] also examined the relationship between vitamin D and renal phosphorus excretion in a normocalcemic, normophosphatemic weanling rat model fed a vitamin D–deficient diet. The animals were mildly vitamin D deficient (92 pg per mL of 1,25-dihydroxycholecalciferol versus 169 pg per mL in controls) but had no evidence of secondary hyperparathyroidism. Clearance studies performed in the basal partially vitamin D–deficient state showed an increase in both absolute and fractional phosphorus excretion compared with controls. Animals that were replenished with 1,25-dihydroxycholecalciferol and maintained on diets designed to protect against the development of hyperphosphatemia demonstrated a significant decrease in urinary phosphorus excretion. Other animals were similarly replenished with vitamin D but did not receive dietary adjustment; and in this group, both the serum phosphorus and the urinary phosphorus excretion level increased significantly. A third group was fed a normal diet and received smaller doses of 1,25-dihydroxycholecalciferol (15 pmol per g of body weight) for shorter periods, and although this dose had no effect on the serum phosphorus concentration, the phosphaturia was completely resolved.

Studies on BBM vesicles prepared from these animals revealed that in the partially vitamin D–deficient state, sodium-dependent phosphorus uptake was significantly reduced compared with control animals. Animals that were replenished with vitamin D and fed a controlled diet had a greater sodium-dependent phosphorus uptake than both vitamin D–depleted and vitamin D–replenished animals not maintained on controlled diets.

The results of this series of studies suggest that the primary action of 1,25-dihydroxycholecalciferol is to increase tubular phosphorus reabsorption. Long-term administration of vitamin D, however, represents a more complex situation, where phosphaturia may occur secondary to changes in the filtered load of phosphorus, in the body distribution of phosphorus, or in intracellular phosphorus activity.

Effects of Changes in Acid–Base Balance on Phosphate Excretion

The effect of acid–base status on the renal excretion and transport of phosphate is complex. Acute respiratory acidosis increases and acute respiratory alkalosis decreases phosphate excretion.[275] These effects occur independently of PTH and plasma or luminal bicarbonate levels.[275] However, other studies suggest that the effects of respiratory acid–base changes may be mediated by changes in plasma phosphate.[275]

Acute metabolic acidosis has minimal effects on phosphate excretion; however, the phosphaturic effect of PTH is blunted.[43] Acute metabolic alkalosis causes an increase in phosphate excretion independently of PTH.[206,345,448,526,530] This effect is due, in part, to volume expansion produced by the infusion of bicarbonate.[448,530]

Chronic acidosis increases phosphate excretion, again independent of PTH or changes in ionized Ca^{2+}.[144,234,345,509] The effect appears to be directly on the sodium-dependent phosphate transport mechanism.[674] Chronic alkalosis decreases phosphate excretion, probably by the same mechanism as acidosis, operating in the opposite direction.[206,535]

Acute and chronic acidosis in rats decreases the proximal tubule cell luminal membrane expression of the NaPi-IIa cotransporter.[18] In acute acidosis, there is rapid internalization of the transporter and the total cortical homogenate cotransporter expression is unchanged. In chronic acidosis, there are parallel changes in NaPi-IIa protein and mRNA abundance. The effects of acid–base perturbations are complex and depend on antecedent dietary intake, the chronicity of the change, and whether the change affects luminal or intracellular pH, or both.

Adrenal Hormones

Administration of pharmacologic amounts of cortisol leads to phosphaturia. Acute adrenalectomy reduces the GFR and increases the reabsorption of phosphorus in the proximal tubule. Frick and Durasene[195] concluded that glucocorticoid hormones could play an important role in the regulation of fractional reabsorption of phosphorus. Indeed administration of glucocorticoids to animals has been shown to decrease proximal tubular NaPi cotransport activity and induce phosphaturia by causing parallel decreases in NaPi-IIa protein and mRNA levels.[370] The inhibitory effects of glucocorticoids in NaPi transport is in part mediated by the concomitant alterations in renal proximal tubular apical BBM glycosphingolipid composition, as inhibition of glycosphingolipid synthesis prevents in part the decrease in renal NaPi cotransport activity. In contrast to glucocorticoid administration, adrenalectomy

with mineralocorticoid administration, resulting in selective glucocorticoid deficiency, is associated with increased renal proximal tubular NaPi-IIa protein expression.[396]

Growth Hormone

An increase in serum phosphorus and a rise in renal phosphorus transport are characteristics of growth hormone (GH) excess during the period of rapid growth in the child, during acromegaly, or during exogenous GH administration to experimental animals. Hammerman et al. reexamined this phenomenon in the BBM vesicle preparation in the dog[252] and demonstrated that GH treatment resulted in an increased sodium-dependent phosphorus transport. These data reassert the importance of BBM phosphorus uptake in regulating overall renal phosphorus reabsorptive capacity. The action of growth hormone is likely mediated by insulin-like growth factor-1.[114]

Studies have further identified the nephron sites and mechanisms by which GH regulates renal Pi uptake.[716] Micropuncture experiments were performed after acute thyroparathyroidectomy in the presence and absence of PTH in adult (14- to 17-week-old), juvenile (4-week-old), and GH-suppressed juvenile male rats. Although the phosphaturic effect of PTH was blunted in the juvenile rat compared with the adult, suppression of GH in the juvenile restored fractional Pi excretion to adult levels. In the presence or absence of PTH, GH suppression in the juvenile rat caused a significant increase in the fractional Pi delivery to the late proximal convoluted (PCT) and early distal tubule, so that delivery was not different from that in adults. These data were confirmed by Pi uptake studies into BBM vesicles. Immunofluorescence studies indicate increased BBM type IIa NaPi cotransporter (NaPi-II) expression in the juvenile compared with adult rat, and GH suppression reduced NaPi-II expression to levels observed in the adult. GH replacement in the [N-acetyl-Tyr(1)-d-Arg(2)]-GRF-(1-29)-NH(2)-treated juveniles restored high NaPi-II expression and Pi uptake. Together, these novel results demonstrate that the presence of GH in the juvenile animal is crucial for the early developmental upregulation of BBM NaPi-II and, most importantly, describe the enhanced Pi reabsorption along the PCT and proximal straight nephron segments in the juvenile rat.[716]

Thyroid Hormone

Because Pi is intensively used in general metabolism, Pi homeostasis should be regulated by factors controlling the rate of metabolism itself. One such factor is thyroid hormone, and its role in Pi reabsorption regulation has been extensively analyzed.[45.637,729] Pharmacologic doses of T_3 have been shown to increase Na/Pi cotransport in BBM vesicles from rat proximal tubules.[54,729] In addition, T_3 concentrations approximating the association constant (K_m) of the thyroid hormone nuclear receptor also elicited a similar increase in P_i transport in opossum kidney (OK) cells.[637] In both cases, the increase in transport rate was caused by an increase in the capacity of the transport system, whereas the affinity was not modified. Euzet et al.[182,183] have shown an important role for T_3 in the maturation of the renal Na/Pi cotransporter, which was associated with changes in both K_m and V_{max}, as well as in the type II Na/Pi cotransporter (NaPi-II) protein and mRNA abundance.

Sorribas et al. have determined the role of physiologic concentrations of thyroid hormone in renal phosphate transport in vivo. In addition, they also determined the potential role of thyroid hormone in impairment of phosphate reabsorption that accompanies the aging kidney.[16] Their results show that chronically treated hypothyroid rats, using a physiologic dose of T_3, exhibit increases in serum Pi levels, NaPi-II mRNA and protein content, and Na/Pi cotransport activity in superficial and juxtamedullary renal cortex, all these effects by means of enhanced transcription of the corresponding NaPi-II gene. The stimulatory effect of the hormone was less evident in the aging kidney, which shows a lower level of basal phosphate reabsorption. In this study, only pharmacologic hyperthyroidism was able to restore partially the level of serum Pi observed in young animals.

Epidermal Growth Factor

Epidermal growth factor (EGF) is a 53-amino acid polypeptide. The kidney is a major site of synthesis of the EGF precursor, prepro-EGF. In renal epithelial cells grown in culture, EGF has been shown to modulate sodium gradient-dependent phosphate transport (Na-Pi cotransport) activity, but the directionality of the modulation in cell culture has been controversial.[22,232,510] A study also determined whether EGF regulates Na-Pi cotransport activity in vivo and whether the effect of EGF to regulate Na-Pi cotransport is dependent on the developmental stage of the animal (i.e., suckling [12-day-old] vs. weaned [24-day-old] rats). This study demonstrated that proximal tubule BBMV Na-Pi cotransport activity, Na-Pi-II protein abundance, and NaPi-II mRNA abundance are higher in weaned than in suckling rats and that EGF inhibits Na-Pi cotransport activity in BBMV isolated from suckling and weaned rats by a decrease in NaPi-II protein abundance, in the absence of a change in NaPi-II mRNA.[23]

Aging

The aging process is associated with impairment in renal tubular reabsorption of Pi and renal tubular adaptation to a low Pi diet. In experiments using 3- to 4-month-old young adult rats and 12- to 16-month-old aged rats, it was found that there was an age-related twofold decrease in proximal tubular apical BBM Na-Pi cotransport activity, which was associated with similar decreases in BBM NaPi-II protein abundance and renal cortical NaPi-II mRNA level. Immunohistochemistry showed lower NaPi-II protein expression in the BBM of proximal tubules of superficial, midcortical, and juxtamedullary nephrons. This study also found that in response to chronic (7 days) and/or acute (4 hour) feeding of a low Pi diet, there were similar adaptive increases in BBM Na-Pi cotransport activity and BBM NaPi-II protein abundance in both young and aged rats. However, BBM Na-Pi cotransport activity and BBM NaPi-II protein abundance were still

significantly lower in aged rats, in spite of a significantly lower serum Pi concentration in aged rats. Thus, impaired expression of the type II renal Na-Pi cotransporter protein at the level of the apical BBM plays an important role in the age-related impairment in renal tubular reabsorption of Pi and renal tubular adaptation to a low Pi diet.[635]

Stanniocalcin

Stanniocalcin is a calcium and phosphate regulating hormone found in serum and the kidney. In teleost fish, it is produced in the corpuscles of Stannius, specialized endocrine organs closely associated with the kidneys. Stanniocalcin plays a major role in the calcium and phosphate homeostasis of fish. It inhibits calcium uptake by the gills and gut and stimulates phosphate reabsorption by the kidney.[151,157,294,406,413,489,680,733]

Two mammalian homologues of Stanniocalcin have been identified. Stanniocalcin 1 and Stanniocalcin 2, with seemingly opposing effects on renal phosphate transport. Stanniocalcin I induces increased gastrointestinal (GI) and renal Pi transport.[295] Stanniocalcin 2 on the other hand causes inhibition of renal Pi transport by transcriptional mechanisms.[295]

Diuretics

Acetazolamide inhibits phosphate reabsorption by its effects on proximal tubule decreases in Na^+-dependent bicarbonate transport, essential for the maintenance of the Na^+ gradient. Furosemide inhibits carbonic anhydrase activity and thus decreases phosphate transport. Similar effects have been demonstrated with the administration of large doses of thiazide diuretics.[246]

Hypophosphatemia

Hypophosphatemia refers to serum phosphorus concentrations of less than 2.5 mg per dL. Hypophosphatemia usually results from one or a combination of the following factors (Fig. 6)[328,340]: (1) increased excretion of phosphorus in the urine; (2) decreased GI absorption of phosphorus; or (3) translocation of phosphorus from the extracellular to the intracellular space. The major causes of hypophosphatemia are shown in Table 73.1.

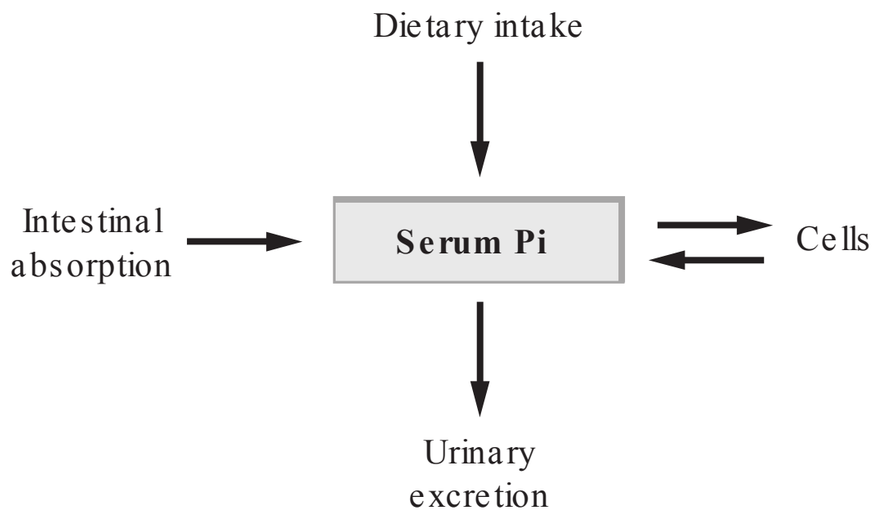


FIGURE 73.6 The major determinants of serum inorganic phosphate (Pi) concentration.

73.1 Causes of Hypophosphatemia

I. Increased excretion of phosphorus in the urine
  A. Familial
  B. Primary hyperparathyroidism
  C. Secondary hyperparathyroidism
  D. Renal tubular defects (Fanconi syndrome)
  E. Diuretic phase of acute tubular necrosis
  F. Postobstructive diuresis
  G. Extracellular fluid volume expansion
    1. X-linked hypophosphatemia
    2. Autosomal dominant hypophosphatemic rickets
    3. Autosomal recessive hypophosphatemic rickets 1; autosomal recessive hypophosphatemic rickets 2
    4. Oncogenic hypophosphatemic osteomalacia (TIO) - Phos
    5. McCune-Albright syndrome/Fibrous dysplasia
    6. Mutations in NaPi-IIa
    7. Hereditary hypophosphatemic rickets with hypercalciuria
  H. Posttransplant hypophosphatemia

II. Decrease in gastrointestinal absorption of phosphorus
  A. Abnormalities of vitamin D metabolism
    1. Vitamin D–deficient rickets
    2. Familial
      a. Vitamin D–dependent rickets
      b. X-linked hypophosphatemia
  B. Malabsorption
  C. Malnutrition-starvation

III. Miscellaneous causes/translocation of phosphorus
  A. Leukemia, lymphoma
  B. Diabetes mellitus: during treatment for ketoacidosis
  C. Severe respiratory alkalosis
  D. Recovery phase of malnutrition
  E. Alcohol withdrawal
  F. Toxic shock syndrome
  G. Severe burns

Increased Excretion of Phosphorus in the Urine

Several pathophysiologic conditions increase excretion of phosphorus in the urine. Some of these are characterized by elevated levels of circulating PTH or FGF23. Because PTH and FGF23 decrease phosphorus reabsorption by the kidney, elevations of the hormones increase urinary excretion (Table 73.1). Decreased tubular reabsorption of phosphorus may also occur without increased levels of PTH and may

be due to changes in the reabsorption of salt and water or to renal tubular defects specific for the reabsorption of certain solutes or phosphorus. Hypophosphatemia may also occur in the diuretic phase of acute tubular necrosis or in postobstructive diuresis, presumably due to a combination of high levels of PTH and decreased tubular reabsorption of salt and water.

Primary Hyperparathyroidism

Primary hyperparathyroidism is a common entity in clinical medicine.[27] PTH is secreted in excess of the physiologic needs for mineral homeostasis due to either adenomas or hyperplasia of the parathyroid glands.[54] This results in decreased phosphorus reabsorption by the kidney. The losses of phosphorus in the urine result in hypophosphatemia. The degree of hypophosphatemia may vary considerably among patients, because mobilization of phosphorus from bone will in part mitigate the hypophosphatemia. Moreover, if the patient ingests large amounts of dietary phosphorus, the degree of hypophosphatemia observed may be mild. Because these patients also have elevated levels of serum calcium, the diagnosis is made relatively easy in most cases by the finding of elevated levels of immunoreactive PTH.

Secondary Hyperparathyroidism

Although secondary hyperparathyroidism is present in most patients with chronic renal disease, hyperphosphatemia rather than hypophosphatemia occurs in such patients because of decreased phosphorus excretion in the urine resulting from the fall in GFR. However, certain conditions characterized by malabsorption of calcium from the GI tract may produce hypocalcemia, leading to development of secondary hyperparathyroidism.[224] The elevated levels of PTH will decrease phosphorus reabsorption by the kidney, resulting in hypophosphatemia. Thus, patients with GI tract abnormalities resulting in calcium malabsorption and secondary hyperparathyroidism will have low levels of serum calcium and phosphorus. In these patients, the hypocalcemia is responsible for the increased release of PTH. In addition, decreased intestinal absorption of phosphorus as a result of the primary GI tract disease may also contribute to the decrement in the levels of serum phosphorus. In general, these patients have

73.2 Inherited Disorders of Phosphate Homeostasis Cause Hypophosphatemic Rickets or Hyperphosphatemia and Are Components of a Bone Kidney Endocrine Axis

Protein/Gene	Function	Disease
FGF23	Hormone regulating phosphate excretion and calcitriol production	ADHR: excess tumoral calcinosis: deficiency
PHEX	Unclear, inhibits FGF23 secretion/production	XLH
DMPI	Matrix protein, inhibits FGF23 secretion/production	ARHR1
ENNPI	Produces pyrophosphate in osteocyte/osteoblast extracellular fluid/inhibits FGF23 secretion/production	ARHR2: homozygous infantile calcific arteriopathy: homozygous
GALNT3	O-glycosylation of FGF23, deficiency increases SPC mediated FGF23 cleavage	Tumoral calcinosis
KLOTHO	FGF23 co-receptor	Tumoral calcinosis Hyperphosphatemia Early senescence
NaPi2c/SLC34A3	Proximal tubule phosphate transport protein	HHRC
CYP27BI	Produces calcitriol which stimulates FGF23 production	Vitamin D dependent rickets
NaPi2a/SLCH34A1	Proximal tubule phosphate transport protein	Nephrolithiasis

FGF23, fibroblast growth factor 23; ADHR, autosomal dominant hypophosphatemic rickets; PHEX, phosphate regulating gene with homologies to endopeptidases on the X chromosome; XLH, x-linked hypophosphatemia; DMPI, dentin matrix protein 1; ARHR1, autosomal recessive hypophosphatemic rickets 1; ENNPI, ectonucleotide pyrophosphatase 1; ARHR2, autosomal recessive hypophosphatemic rickets 2; GALNT3, N- acetylglucosaminyltransferase 3; SLC34A3, solute carrier family 34A3; HHRC, hereditary hypophosphatemic rickets with calciuria; CYP27BI, cytochrome P450 family 27 subfamily B polypeptide I.

urinary losses of phosphorus that are out of proportion to the hypophosphatemia in contrast to patients with predominant phosphorus malabsorption and no secondary hyperparathyroidism in whom urinary excretion of phosphorus is low.

Familial Hypophosphatemia

Studies of hereditary (Table 73.2), and acquired (oncogenic hypophosphatemic osteomalacia [OHO] and McCune-Albright syndrome) renal phosphate wasting disorders have led to the identification of novel genes involved in the regulation of renal Pi transport and calcitriol synthesis.[70,87,536,537,561,579,659] The discovery of these genes has established a bone-kidney axis responsible for maintaining phosphate homeostasis (Fig. 73.5).

X-linked Hypophosphatemia

X-linked hypophosphatemia (XLH) is a common cause of rickets with a prevalence of approximately 1 in 20,000. It is inherited in an X-linked dominant manner. Manifestations of XLH include short stature, bone pain, tooth abscesses, calcification of tendon insertions, ligaments, joint capsules, and lower extremity deformities. However, with genetic sequencing causing reclassification of some presumed XLH patients into autosomal dominant hypophosphatemic rickets (ADHR) or autosomal recessive hypophosphatemic rickets (ARHR) categories, the clinical manifestations may change. For example, posterior longitudinal ligament ossification may be a manifestation mainly of ARHR2.[379] XLH is characterized by hypophosphatemia, decreased reabsorption of phosphorus by the renal tubule, decreased absorption of calcium and phosphorus from the GI tract, and varying degrees of rickets or osteomalacia. Patients with this disorder exhibit normal to reduced levels of 1,25-dihydroxycholecalciferol despite hypophosphatemia and reduced Na-phosphate transport in the proximal tubule. The message levels of NaPi-IIa are reduced by 50% in the PCT of Hyp mice similar to the reduction in apical membrane vesicle NaPi-IIa protein levels.[663]

The gene responsible for XLH was designated **PHEX** for **PH**osphate regulating gene with homology to **E**ndopeptidases on the **X** chromosome.[3] PHEX is a member of the M13 family of type II cell surface zinc-dependent metallopeptidases which includes neprilysin, endothelin-converting enzymes 1 and 2, KELL, and DINE/X-converting enzyme. The mouse PHEX DNA sequence is highly homologous to that of humans and the inactivating mutations of PHEX have been identified in the mouse homologues of XLH, Hyp and Gy mice. More than 180 mutations in the PHEX gene have been shown to result in XLH. PHEX is expressed predominantly in osteoblasts, osteocytes, and odontoblasts, but not in the kidney. The hypophosphatemia and rickets of XLH is produced by excess FGF23 in the circulation.[307,726] How PHEX inactivation variably increases FGF23 secretion is currently unknown (Fig. 73.5). However, the finding that homozygous ablation of FGF23 in the Hyp background produced the phenotype of FGF23 deficiency (hyperphosphatemia, elevated calcitriol, and vascular calcification) and loss of the Hyp phenotype demonstrates that FGF23 is causative of hypophosphatemia in Hyp and XLH.[619] The initial thought that FGF23 was a PHEX substrate[84] proved untrue.[47,244,392,393] In fact, FGF23 has recently been shown to be cleaved by subtilisin-like protein convertases (SPC) (Fig. 73.5). SPCs are a seven-member family of calcium-dependent serine proteases responsible for the processing of peptide hormones, neuropeptides, adhesion molecules, receptors, growth factors, cell surface glycoproteins, and enzymes. Instead PHEX, most likely through the actions of unidentified PHEX substrates or other downstream effectors, regulates FGF23 secretion as part of a hormonal axis between bone and kidneys that controls systemic phosphate homeostasis and mineralization.[47]

From a therapeutic point of view, the combination of neutral phosphate and 1,25-dihydroxycholecalciferol has led to an improvement in the bone disease of patients with XLH and in the Hyp mice.[225,676] The administration of phosphorus in X-linked hypophosphatemia is usually divided into four doses, with the total amount ranging between 1 to 4 g per day. Pharmacologic doses of 1,25-dihydroxycholecalciferol on the order of 1 to 3 μg per day may be necessary to correct the skeletal alterations. 1,25-dihydroxycholecalciferol does not correct the increased fractional excretion of phosphate. The enthusiasm for this regimen is tempered by a high incidence of nephrocalcinosis and occasional renal failure.[196,225,676]

Autosomal Dominant Hypophosphatemic Rickets

The clinical presentation of ADHR is similar to XLH. However, ADHR exhibits male to male transmission, consistent with autosomal dominant inheritance, and is characterized by incomplete penetrance and variable age of onset. Adults typically complain of bone pain, fatigue, and/or weakness, and can present with stress fractures or pseudofractures. Renal phosphate wasting and inappropriately normal serum calcitriol levels are the most typical laboratory findings.

The gene responsible for ADHR is a member of the FGF family, FGF23.[4] FGF23 is a 251 amino acid peptide secreted by osteocytes and processed to amino- and carboxy-terminal peptides at a consensus pro-protein convertase (furin) site. In four unrelated ADHR families missense mutations have been identified in FGF23 in the proteolytic cleavage site (R176Q, R179W, and R179Q) that interfere with peptide processing and result in gain of function of FGF23.[603,712,713]

Administration of wild-type FGF23 or FGF23 expressing the ADHR mutations in the furin cleavage site (R176Q, R179W, or R179Q) to rats and mice has been shown to induce hypophosphatemia, increased urinary phosphate excretion via inhibition of the type IIa NaPi cotransport protein, and decreased 1,25 $(OH)_2D_3$ levels.[36,572,586,600] Chronic administration of FGF23 and increased expression of FGF23 (FGF23 transgenic mice) has also been shown to induce osteomalacia and decreased 1,25 $(OH)_2D_3$ levels via decrease in 25-hydroxyvitamin D 1α-hydroxylase mRNA.[35,353,604]

In vitro studies in OK cells have demonstrated that FGF23 inhibits Na/Pi cotransport activity and type IIa NaPi cotransport protein abundance by the MAPK signaling dependent pathway.[725]

In contrast, targeted ablation of FGF23 in mice results in significantly increased serum Pi levels with increased renal Pi absorption. These mice also have increased serum 1,25 $(OH)_2D_3$ levels that is due to increased expression of renal 25-hydroxyvitamin D 1α-hydroxylase (1α-OHase).[601] Another study with homozygous ablation of FGF23 in mice revealed that these mice have marked hyperphosphatemia, increased serum 1,25 $(OH)_2D_3$ levels, growth retardation, increased total body bone mineral content but decreased bone mineral density of the limbs, and excessive mineralization in soft tissues, including in the heart, vasculature, and kidneys.[619]

Autosomal Recessive Hypophosphatemic Rickets

Genetic studies have led to the discovery of autosomal recessive inheritance familial hypophosphatemic rickets. The genes involved are dentin matrix protein 1 (DMP1) in ARHR1, and ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) in ARHR2 (Fig. 73.5).[188,400,401] Circulating levels of FGF23 are elevated in ARHR1 and 2, and FGF23 is thought to be the basis of the hypophosphatemia and rickets. The clinical picture of ARHR resembles that of ADHR and XLH. Therefore, genetic studies may be needed in the future to establish molecular etiology of hypophosphatemic rickets.

Oncogenic Hypophosphatemic Osteomalacia or Tumor-Induced Osteomalacia

Tumor-induced osteomalacia (TIO) is an acquired disorder of renal phosphate wasting with clinical and biochemical features similar to XLH and ADHR. This disorder is characterized by hypophosphatemia associated with tumors. It was described initially in association with benign mesenchymal tumors; however, other reports have emphasized the association of this syndrome with malignant tumors.[501,565] The other characteristics of this syndrome are increased phosphate excretion, low plasma 1,25-dihydroxycholecalciferol concentrations, and osteomalacia. All of the biochemical and pathologic abnormalities disappear when the tumor is resected.

The tumors associated with this syndrome have been found to secrete substances that inhibit the renal tubular reabsorption of phosphate and suppress 25-hydroxycholecalciferol 1α-hydroxylase activity. The TIO substances include FGF23, MEPE, sFRP4, and others.[53] FGF23 has been cloned from the tumors of patients who have presented with TIO and FGF23 is the most prevalent factor causing both the impaired renal Pi reabsorption resulting in hypophosphatemia and also the decreased serum 1,25 $(OH)_2D_3$ levels.[150,602,648] Several studies have shown increased serum levels of FGF23 and/or immunohistochemical detection of FGF23 in patients who present with TIO and the serum levels to normalize after the resection of the tumors.[193,354,479,656,688] sFRP-4 has been detected in patients with TIO and it has been shown to inhibit Pi transport in OK cells and also in normal rats by PTH-independent mechanisms.[53] sFRP-4 antagonizes Wnt signaling but at this time the role of the Wnt pathway in regulation of renal Pi transport or 25-hydroxyvitamin D 1α-hydroxylase has not been established.

MEPE is exclusively expressed in osteoblasts, osteocytes, and odontoblasts and is markedly upregulated in murine XLH (Hyp) osteoblasts and TIO tumors (Fig. 73.5).[24,90,300,561,562] The recombinant human-MEPE has been shown to result in dose-dependent inhibition of renal Pi reabsorption, phosphaturia, and hypophosphatemia.[564] In addition, human-MEPE dose dependently inhibited BMP-2 mediated mineralization of a murine osteoblast cell line (2T3) in vitro.[563]

A protease-resistant carboxy-terminal MEPE peptide containing the acidic serine-aspartate rich motif (ASARM) peptide has been shown to play a role in the inhibition of the mineralization (minhibin). PHEX prevents proteolysis of MEPE and release of ASARM. In XLH mutated PHEX may, therefore, contribute to the increased ASARM peptide seen in that disorder.[563] Recent studies using surface plasmon resonance (SPR) indicates that MEPE binds to PHEX via the MEPE-ASARM motif which can provide a molecular basis for the inhibition of bone mineralization in XLH subjects and Hyp mice.[563] The potential role of ASARM in regulation of renal Pi transport or 25-hydroxyvitamin D 1α-hydroxylase, however, remains to be determined.

In contrast to the potential role of MEPE and ASARM to inhibit bone mineralization, disruption of MEPE gene in mice results in increased bone mass, resistance to age-associated trabecular bone loss, increased mineralization apposition rate, and accelerated mineralization in ex vivo osteoblast cultures.[233] These mice, however, have normal serum Pi levels, perhaps due to normal FGF23 and PHEX expression.

McCune-Albright Syndrome and Fibrous Dysplasia

McCune-Albright syndrome (MAS) is characterized by the clinical triad of polyostotic fibrous dysplasia (FD), café au lait skin pigmentation, and endocrine/metabolic disorders. The endocrine disorders include autonomous secretion of various hormones such as GH, thyroid hormone, cortisol, estradiol, and testosterone. Rickets and osteomalacia due to hyperphosphaturic hypophosphatemia are prominent components of the syndrome.[14,58,59,134,140,146,386,387,443,551,569,704]

The disorders of the syndrome share in common excessive function of cells whose actions are normally regulated by hormones that induce cAMP generation. The molecular basis for the phenotype is an activating mutation of GNAS1 which encodes the $G_S\alpha$ protein (α component of

the stimulatory heterotrimeric guanosine triphosphate binding protein, G_S) in cells from affected tissues from patients with the syndrome.[14,58,59,134,140,146,386,387,443,551,569,704] Kidney tissue, presumably proximal tubule, from patients has been reported to contain cells with the mutation.

A study using a combination of real-time polymerase chain reaction (RT-PCR), in situ hybridization, enzyme-linked immunosorbent assay (ELISA) of media conditioned by normal and FD stromal cells and trabecular bone cells, and measurements of FGF23 in the serum has determined that FGF23 is expressed in FD tissues and osteogenic cells and that high levels of circulating FGF23 correlate with renal Pi wasting in FD/MAS patients.[550]

Mutations in the Type IIa NaPi Cotransporter (SLC34A1)

Epidemiologic studies suggest that genetic factors confer a predisposition to the formation of renal calcium stones or bone demineralization. Low serum phosphate concentrations due to a decrease in renal phosphate reabsorption have been reported in some patients with these conditions, suggesting that genetic factors leading to a decrease in renal phosphate reabsorption may contribute to them. Prie and colleagues investigated if mutations in the gene coding for the main renal sodium-phosphate cotransporter (NaPi-IIa) may be present in patients with these disorders. Twenty patients with urolithiasis or bone demineralization and persistent idiopathic hypophosphatemia associated with a decrease in maximal renal phosphate reabsorption were studied. The coding region of the gene for NaPi-IIa was sequenced in all patients. The functional consequences of the mutations identified were analyzed by expressing the mutated RNA in Xenopus laevis oocytes. Two patients, one with recurrent urolithiasis and one with bone demineralization, were found to be heterozygous for two distinct mutations. One mutation resulted in the substitution of phenylalanine for alanine at position 48, and the other in a substitution of methionine for valine at position 147. Phosphate-induced current and sodium-dependent phosphate uptake were impaired in oocytes expressing the mutant NaPi-IIa. Coinjection of oocytes with wild-type and mutant RNA indicated that the mutant protein had altered function. This study, therefore, concluded that heterozygous mutations in the NaPi-IIa gene may be responsible for hypophosphatemia and urinary phosphate loss in persons with urolithiasis or bone demineralization.[520]

A follow-up study by Virkki and colleagues recreated the two mutants, expressed them in Xenopus oocytes, and analyzed their kinetic behavior by two-electrode voltage clamp. They also performed coexpression experiments where they injected mRNA for wild-type (WT) and mutants containing an additional S462C mutation, enabling complete inhibition of cotransport function with cysteine-modifying reagents. Finally, WT and mutant NaPi-IIa as C-terminal fusions to green fluorescent protein (GFP) in opossum kidney (OK) cells was expressed They found in oocyte expression experiments that Pi-induced currents were reduced in both mutants, whereas Pi and Na affinities and other transport characteristics were not affected. The amount of cotransport activity remaining after cysteine modification, corresponding to WT activity, was not affected by coexpression of either mutant. Finally, GFP-tagged WT and mutants were expressed at the apical membrane in OK cells, showing that both mutants are correctly targeted in a mammalian cell.[679] This, therefore, suggests that the heterozygous A48F and V147M mutations cannot explain the pathologic phenotype observed by Prie and colleagues. In this regard Prie and colleagues reported mutations in NaPi-IIa interacting PDZ domain containing protein NHERF1 that result in renal phosphaturia.[312,372,518,519] In addition Magen and Skorecki and colleagues have also reported a loss of function mutation in NaPi-IIa in ARHR with renal Fanconi syndrome.[415]

Mutations in the Type IIc NaPi Cotransporter (SLC34A3)

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is an autosomal form of hypophosphatemic rickets.[666] The gene involved in HHRH is NaPi-IIc (SLC34A3). The disease is characterized, and differs from other forms of hereditary hypophosphatemic rickets and/or osteomalacia, by increased serum levels of 1,25-dihydroxyvitamin D, increased GI calcium absorption, and hypercalciuria. Some of the NaPi-IIc mutations cause mistargeting of NaPi-IIc protein and uncoupling of NaPi cotransport activity.[50,301,371,658]

Renal Tubular Defects

Several conditions characterized by single or multiple tubular defects have been described in which phosphorus reabsorption is decreased. In the Fanconi syndrome,[559] patients excrete not only increased amounts of phosphorus in the urine but also increased quantities of amino acids, uric acid, and glucose, resulting in hypouricemia and hypophosphatemia. Rare familial forms of hypercalciuria are often associated with one or more of the components of the Fanconi syndrome including hypophosphatemia or hyperphosphaturia.[210,394,665] Interestingly, these familial syndromes, Dent disease, and its variants have been found to be caused by a mutation in the CLCN5 chloride channel,[394,578] which is an intracellular vesicular channel, perhaps related to the vesicles that harbor the NaPi cotransport proteins.[242,304,305,331] There are other conditions in which an isolated defect in the renal tubular transport of phosphorus has been found, for example, fructose intolerance, which is an autosomal-recessive disorder.[278] After renal transplantation, an acquired renal tubular defect may be responsible for the persistence of hypophosphatemia in some patients.[366,556]

Diuretic Phase of Acute Tubular Necrosis

Most patients with acute renal failure develop secondary hyperparathyroidism and hyperphosphatemia during

the oliguric phase. During the recovery phase of acute renal failure, the combined occurrence of a profound diuresis, secondary hyperparathyroidism, and continued use of phosphate binders may lead to severe hypophosphatemia. This hypophosphatemia is usually short lived, and serum phosphorus levels return to within the normal range as the diuretic phase of acute tubular necrosis subsides.

Postobstructive Diuresis

A marked phosphaturia may develop in some patients after relief of urinary tract obstruction. This phosphaturia may be severe enough in a few patients to lead to hypophosphatemia.[185]

Extracellular Fluid Volume Expansion

Expansion of the ECF volume by the administration of solutions containing sodium increases the urinary excretion of phosphorus. An important mechanism by which ECF volume expansion produces phosphaturia consists of a fall in ionized calcium and subsequent release of PTH.[42] This condition is probably of minor importance in clinical medicine, and restoration of the ECF volume to within the normal range results in the return of phosphorus reabsorption to physiologic levels.

Posttransplant Hypophosphatemia

Posttransplant hypophosphatemia, a common disorder, is well described in the literature. Although described mainly in patients following renal transplantation,[56,208,234,245,458,488,492,500,555,574,643,687] posttransplant hypophosphatemia also occurs in patients undergoing bone marrow transplantation.[143,538] In all reports, the decrease in serum Pi concentration was associated with an increase in urinary phosphate excretion and a significant decrease in the measured or derived ratio of maximal rate of renal tubular transport of phosphate to glomerular filtration rate (TmPi/GFR).[684] In addition to the impairment in renal tubular phosphate reabsorption, evidence indicates that intestinal phosphate absorption is impaired in transplant patients.[186,366,429,557]

The mechanism for posttransplant hypophosphatemia has not been fully elucidated, but it is linked to disordered regulation of renal tubular reabsorption of Pi. As discussed earlier, PTH leads to a reduction in the expression of type II Na/Pi cotransport at the BBMs, which accounts for the phosphaturic action of PTH. Given this property of PTH, it has been postulated that increased PTH activity during chronic renal failure (CRF) may be the major mechanism responsible for maintaining Pi balance during CRF. According to this hypothesis, posttransplant hypophosphatemia has been attributed to persistent hyperparathyroidism (HPT), that is, incomplete involution of hyperplastic glands produced by renal failure prior to transplantation would cause hypophosphatemia and increased phosphaturia during the early posttransplant period.[262] Several studies, however, have documented that protracted HPT cannot account for the phenomenon of posttransplant hypophosphatemia since it can be seen in transplant patients with normal PTH levels. Moreover, transplant recipients failed to decrease Pi excretion in the urine even when PTH was suppressed by calcium infusion.[555] In addition, the phosphaturia following kidney transplantation could not be ascribed to the effects of nephrectomy or to the influence of immunosuppressive drugs.[555]

A study by Green et al. determined that a non-PTH humoral mechanism accounted for the entity of posttransplant hypophosphatemia.[237] The factor, however, had characteristics different from FGF-23, sFRP-4, and MEPE, phosphatonins discussed earlier.[237] However, recent studies continue to focus on PTH and FGF23 as the causes of posttransplant hypophosphatemia in the early posttransplant period.

Decrease in Gastrointestinal Absorption of Phosphorus

Abnormalities of Vitamin D Metabolism

Vitamin D and its metabolites play an important role in phosphorus homeostasis.[236] Vitamin D promotes the intestinal absorption of calcium and phosphorus and is necessary to maintain the normal mineralization of bone. Dietary deficiencies of vitamin D increase the amount of osteoid tissue in the skeleton and decrease normal mineralization. Bone mineralization is a complex process that is not completely understood. Normally, the osteoblast is responsible for laying down normal collagen that is well organized and distributed in a lamellar fashion. Between the recently deposited collagen and the old bone, there is an area called the mineralization front. Initially, amorphous calcium phosphate is deposited in the mineralization front and eventually matures into hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$]. Thus, the osteoid tissue changes into bone. Optimal mineralization requires the following: (1) normal bone cell activity; (2) normal supply of minerals; (3) the appropriate pH level (7.4 to 7.6); (4) normal synthesis and composition of the matrix; and (5) control of inhibitors of calcification.

The appositional growth rate in normal bone is about 1 μm per day and complete mineralization of the osteoid requires 13 to 21 days. Thus, the thickness of the osteoid usually does not exceed 20 μm. Less than 20% of the surface of the bone is normally covered by osteoid. When a biopsy is performed in a healthy subject who has previously ingested two doses of tetracycline separately and 3 weeks apart, one usually detects two fluorescent rings or bands, indicating the locations of the mineralization front. In a patient with osteomalacia, usually a single band, no band, or an irregular and spotty uptake of tetracycline is seen. In rickets or osteomalacia, there is a quantitative and qualitative defect in bone mineralization.

Vitamin D–Deficient Rickets

Diets deficient in vitamin D lead to the metabolic disorder known as rickets when it occurs in children or osteomalacia when it appears in adults.[480] Vitamin D deficiency in childhood results in severe deformities of bone because of rapid

growth. These deformities are characterized by soft loose areas in the skull known as craniotabes and costochondral swelling or bending (known as rachitic rosary). The chest usually becomes flattened, and the sternum may be pushed forward to form the so-called pigeon chest. Thoracic expansion may be greatly reduced with impairment of respiratory function. Kyphosis is a common finding. There is remarkable swelling of the joints, particularly the wrists and ankles, with characteristic anterior bowing of the legs, and fractures of the "greenstick" variety may also be seen. In adults, the symptoms are not as striking and are usually characterized by bone pain, weakness, radiolucent areas, and pseudofractures. Pseudofractures represent stretch fractures in which the normal process of healing is impaired because of a mineralization defect. Mild hypocalcemia may be present; however, hypophosphatemia is the most frequent biochemical alteration. This metabolic abnormality responds well to administration of small amounts of vitamin D.

Vitamin D–Dependent Rickets

These are recessively inherited forms of vitamin D–refractory rickets. The conditions are characterized by hypophosphatemia, hypocalcemia, elevated levels of serum alkaline phosphatase, and, sometimes, generalized aminoaciduria and severe bone lesions. Currently, two main forms of vitamin D–dependent rickets have been characterized. The serum concentrations of 1,25-dihydroxycholecalciferol serves to differentiate the two types of vitamin D–dependent rickets.

Type I vitamin D–dependent rickets is associated with reduced calcitriol levels. It is caused by a mutation in the gene converting 25(OH)D to 1,25-dihydroxycholecalciferol, the renal 1α-hydroxylase enzyme.[178,202] This condition responds to very large doses of vitamin D_2 and D_3 (100 to 300 times the normal requirement of physiologic doses), or to 0.5 to 1.0 μg per day of 1,25-dihydroxycholecalciferol.

Type II vitamin D–dependent rickets is characterized by end-organ resistance to 1,25-dihydroxycholecalciferol. Plasma levels of 1,25-dihydroxycholecalciferol are elevated. This finding, in association with radiographic and biochemical signs of rickets, implies resistance to 1,25-dihydroxycholecalciferol in the target tissues. Cellular defects found in patients with vitamin D–resistant rickets type II are heterogeneous, providing in part an explanation for the different clinical manifestations of this disorder. Among the cellular defects are (1) decreased number of cytosolic receptors, (2) deficient maximal hormonal binding, (3) deficient hormone binding affinity, (4) normal hormonal binding but undetectable nuclear localization, and (5) abnormal DNA binding domain for the 1,25-dihydroxycholecalciferol receptor.[385]

Numerous studies[119,187,264,266,419,445,544,632] have demonstrated that hereditary type II vitamin D–resistant rickets is a genetic disease affecting the vitamin D receptor (VDR). Defects in the hormone binding domain[119,187] and the DNA binding domain[266,419] have been defined. In addition, several cases of human vitamin D–resistant rickets have been studied and no abnormality in the coding region of the VDR has been found,[264] suggesting a defect elsewhere in the hormone action pathway. An unexplained feature of this disease in adolescents is the tendency for calcium levels to normalize and for the radiographic abnormalities of rickets to improve, thus giving the appearance that they outgrow the disease. Human vitamin D–resistant rickets as a genetic defect in the VDR varies significantly from other genetic diseases of steroid hormone receptors caused by resistance to thyroid hormone, androgens, and estrogens.[445,544,632] For example, individuals heterozygous for VDR mutations are apparently completely healthy. Secondly, no dominant negative mutations, which are prominent in thyroid hormone resistance, have been identified as a cause of human vitamin D–resistant rickets. Thus, much remains to be learned from the genetic analysis of this disease. The treatment of this condition requires large pharmacologic doses of calcium, which overcome the receptor defects and maintain bone remodeling.[266] Studies in mice with targeted disruption of the VDR gene, an animal model of vitamin D–dependent rickets type II, confirm that many aspects of the clinical phenotype are due to decreased intestinal ion transport and can be overcome by adjustments of dietary intake.[382]

Malabsorption

Because most of the absorption of phosphorus from the GI tract occurs in the duodenum and jejunum, gastrointestinal tract disorders such as celiac disease, tropical and nontropical sprue, and regional enteritis may decrease the absorption of phosphorus.[224] Phosphorus malabsorption has also been described in patients who have undergone surgical bypass procedures for morbid obesity. The degree of hypophosphatemia varies among patients with intestinal malabsorption, being extremely mild in some and severe in others.

Malnutrition

Most of the phosphorus ingested in the diet is present in protein, particularly meat, cheese, milk, and eggs. In many parts of the world where protein consumption is extremely low, hypophosphatemia occurs predominantly in children. Overall growth is retarded and a series of metabolic abnormalities are present.[324]

Administration of Phosphate Binders

Certain compounds, mainly aluminum salts (aluminum hydroxide, aluminum carbonate gel) and calcium carbonate, are used in the treatment of hyperphosphatemia.[598] However, when these compounds are given in excess, they may produce profound hypophosphatemia. These gels trap phosphorus in the small intestine and increase the amount of phosphorus in the stool. Patients ingesting large amounts of phosphate binders and not followed closely may develop phosphate depletion. With time, such individuals may develop severe weakness, bone pain, and osteomalacia.

Miscellaneous Causes of Hypophosphatemia

Major reviews of the causes of hypophosphatemia in hospitalized patients[309,352] attributed most instances to intravenous administration of carbohydrate. However, many other causes were found, including diuretic usage, hyperalimentation, alcoholism, respiratory alkalosis, and use of phosphate binders.[55] A 31% incidence of hypophosphatemia was seen in patients admitted to a general medical ward, and a further fall in serum concentrations occurred in all patients with acute alcoholism between the second and fifth day after admission to a medical ward.[570] Hypophosphatemia is also seen frequently during treatment of diabetic ketoacidosis.[587] When diabetic patients develop ketoacidosis, they usually have an increase in phosphate excretion in the urine; however, the serum phosphate level may be slightly elevated due to acidosis. During the administration of insulin, there is a rapid decrease in the level of glucose with translocation of phosphate from the extracellular to the intracellular space, resulting in hypophosphatemia.

Acute respiratory alkalosis decreases urinary phosphate excretion but produces marked hypophosphatemia.[465] In contrast, patients who receive sodium bicarbonate excrete large amounts of phosphate in the urine; however, the hypophosphatemia that may develop is only moderate in nature. It has been postulated that in respiratory alkalosis, there is an increase in the intracellular pH level with activation of glycolysis and increased formation of phosphate-containing sugars, leading to a precipitous fall in the concentration of serum phosphorus. The mild hypophosphatemia that may be seen during administration of sodium bicarbonate is probably secondary to increased renal phosphate excretion due to a decrease in ionized calcium and release of PTH, as well as to the consequences of ECF volume expansion.

In addition, new clinical disorders have been identified in which hypophosphatemia is an important aspect of the pathologic condition. Marked hypophosphatemia has been associated with acute leukemia or with lymphomas in the leukemic phase.[8,435,730] These individuals typically present with hypophosphatemia, normocalcemia, and no evidence of excess PTH activity. Urinary phosphate concentration is typically extremely low. Although kinetic studies have not been performed in this setting, the facts that serum phosphate concentration correlates with a growth phase of the tumors and that hyperphosphatemia is seen when cells are destroyed by chemotherapy or radiotherapy strongly suggest that serum phosphorus was initially used in the rapid growth of new cells. Because these patients are often severely ill and under treatment with glucose infusions, as well as antacids and other drugs known to induce hypophosphatemia, they may be at great risk of developing severe acute phosphorus depletion.

Another clinical condition in which hypophosphatemia has been a prominent feature is the toxic shock syndrome. Chesney et al.[124] described 22 women with this disorder who showed hypocalcemia and hypophosphatemia as prominent manifestations. Whether respiratory alkalosis or staphylococcal sepsis–induced release of substances were responsible for acute phosphorus shifts into cells is unknown. Lindquist et al.[363] studied in a prospective fashion the importance of hypophosphatemia in patients with severe burns. In 33 patients studied for 2 weeks after injury, transient hypophosphatemia was seen in the second to tenth day in all these individuals. Five of seven patients who died from complications of the terminal injury had severe hypophosphatemia. Because urinary phosphorus excretion was not increased, tissue uptake seems to be the predominant mechanism responsible for the hypophosphatemia. Levy[378] reported the occurrence of severe hypophosphatemia during the rewarming phase in a profoundly hypothermic patient. In this individual, urinary excretion of phosphorus was minimal, suggesting that a shift of phosphate into the cells occurred as a result of rewarming. Finally, the development of hypophosphatemia resulting from refeeding clinically starved patients has been emphasized. Silvis et al.[612] showed that the classic phosphorus-depletion syndrome, consisting of paresthesias, weakness, seizures, and hypophosphatemia, can occur in individuals who receive oral caloric supplements after a prolonged period of starvation. To further evaluate this issue, they performed studies in normal dogs that had been starved or had received normal diets and found that the infusion of calories through an intragastric catheter to previously starved animals resulted in a fall in serum phosphorus concentration from an average of 4.8 mg per dL to 1.6 mg per dL. Nearly 50% of starved animals developed clinical signs of phosphate depletion after oral refeeding. Weinsier and Krumdiek reported two patients who developed the phosphorus-depletion syndrome in association with cardiopulmonary decompensation following overzealous hyperalimentation after prolonged caloric deprivation.[701]

Clinical and Biochemical Manifestations of Hypophosphatemia

The manifestations of hypophosphatemia are presented in Table 73.3. It has been suggested that the clinical manifestations of hypophosphatemia and severe phosphorus depletion are related to disturbances in cellular energy and metabolism. Studies have examined the effects of phosphate depletion on cellular energetics and other components of cell function. A study of glycolytic intermediates and adenine nucleotides during insulin treatment of patients with diabetic ketoacidosis emphasized the important effects of insulin-induced cellular phosphate depletion on cell metabolism.[337] These results demonstrated that the reduced level of 2,3-diphosphoglycerate (2,3-DPG) seen during insulin treatment of diabetes is due to intracellular phosphorus depletion, producing a decrease in glyceraldehyde 3-phosphate dehydrogenase activity rather than inhibition of the phosphofructokinase enzyme system. Ditzel[163] has suggested that repeated transient decreases in red cell oxygen delivery due to reduced 2,3-DPG with insulin-induced hypophosphatemia could contribute over many years to the microvascular

73.3 Clinical and Biochemical Manifestations of Marked Hypophosphatemia

I. Cardiovascular and skeletal muscle
  A. Decreased cardiac output
  B. Muscle weakness
  C. Decreased transmembrane resting potential
  D. Rhabdomyolysis
II. Carbohydrate metabolism
  A. Hyperinsulinemia
  B. Decreased glucose metabolism
III. Hematologic alterations
  A. Red blood cells
    1. Decreased adenosine triphosphate (ATP) content
    2. Decreased 2,3-DPG
    3. Decreased P_{50}
    4. Increased oxygen affinity
    5. Decreased lifespan
    6. Hemolysis
    7. Spherocytosis
  B. Leukocytes
    1. Decreased phagocytosis
    2. Decreased chemotaxis
    3. Decreased bactericidal activity
  C. Platelets
    1. Impaired clot retraction
    2. Thrombocytopenia
    3. Decreased ATP content
    4. Megakaryocytosis
    5. Decreased lifespan
IV. Neurologic manifestations
  A. Anorexia
  B. Irritability
  C. Confusion
  D. Paresthesias
  E. Dysarthria
  F. Ataxia
  G. Seizures
  H. Coma
V. Skeletal abnormalities
  A. Bone pain
  B. Radiolucent areas (X-ray)
  C. Pseudofractures
  D. Rickets or osteomalacia
VI. Biochemical and renal manifestations
  A. Low parathyroid hormone levels
  B. Increased $1,25(OH)_2D_3$
  C. Hypercalciuria
  D. Hypomagnesemia
  E. Hypermagnesuria
  F. Hypophosphaturia
  G. Decreased glomerular filtration rate
  H. Decreased T_m for bicarbonate
  I. Decreased renal gluconeogenesis
  J. Decreased titratable acid excretion
  K. Increased creatinine phosphokinase
  L. Increased aldolase

From Slatopolsky E. Pathophysiology of calcium, magnesium, and phosphorus. In: Klahr S, ed. The Kidney and Body Fluids in Health and Disease. New York: Plenum Press; 1983:269, with permission.

disease seen in diabetic patients. Patients with mild degrees of hypophosphatemia are usually asymptomatic. However, if hypophosphatemia is severe—that is, if serum phosphorus levels are less than 1.5 mg per dL—a series of hematologic, neurologic, and metabolic disorders may develop. In general, the patients become anorectic and weak, and mild bone pain may be present if the hypophosphatemia persists for several months (Table 73.3).

Cardiovascular and Skeletal Muscle Manifestations

Severe cardiomyopathy with decreased cardiac output has been described in patients and animals with severe hypophosphatemia.[484,731] Studies revealed that the resting muscle membrane potential fell, sodium chloride and water content of the tissue increased, and potassium content decreased in severe hypophosphatemia.[205] These values returned to within the normal range after phosphate was administered. Skeletal muscle weakness and electromyographic abnormalities are associated with chronic hypophosphatemia and phosphate depletion. Dogs that were fed low-phosphate diets for several months developed changes in muscle, rhabdomyolysis, and characteristic increases in their levels of creatinine kinase and aldolase in blood.[329] Rhabdomyolysis has been observed in alcoholic patients with hypophosphatemia.[330] Knochel et al.[329] showed that myopathy associated with phosphate depletion in dogs did lead to changes in cell water content, sodium concentration, and transmembrane potential difference. Kretz et al.[341] examined the possibility that changes in calcium transport in the sarcoplasmic reticulum of muscle were responsible for the clinical myopathy seen in acute phosphate depletion. Despite significant hypophosphatemia and a reduction in muscle phosphorus concentration, they found no significant changes in the rate of calcium uptake of calcium-concentrating ability in vesicles prepared from muscle sarcoplasmic reticulum of phosphate-depleted rats. Thus, the role of altered transcellular calcium

movements in phosphate-depleted tissues is yet to be completely resolved.

Effects on Carbohydrate Metabolism

Hyperinsulinemia and abnormal glucose metabolism suggesting insulin resistance have been described in phosphate depletion. DeFronzo and Lange[155] have used the glucose and insulin clamp technique to study the kinetics of glucose metabolism in patients with various chronic hypophosphatemic conditions including vitamin D–resistant rickets. When glucose was infused to maintain constant glycemia at 125 mg per dL, hypophosphatemic individuals required 36% less glucose to maintain these glycemic levels than controls. Also when euglycemia was achieved by combined insulin and glucose infusion, the hypophosphatemic individuals required 40% less glucose to maintain euglycemia than controls. Insulin catabolism was apparently unaffected in these hypophosphatemic individuals. These data indicate that hypophosphatemia is associated with impaired glucose metabolism in both hyperglycemic and euglycemic patients.

Hematologic Manifestations

Hematologic abnormalities of hypophosphatemia are a major manifestation of this syndrome.[388,668] In addition to defects in affinity of oxyhemoglobin leading to generalized tissue hypoxia, there may be increased hemolysis.[298,327] Quantitative and functional defects have also been described in platelets and leukocytes.[142] These defects lead to diminished platelet aggregation and abnormalities in chemotaxis and phagocytosis of white blood cells. The latter may contribute to the increased risk of gram-negative sepsis reported in hypophosphatemic patients.[549] This is of particular concern in immunosuppressed patients receiving phosphate-poor alimentation through a central venous line.

Neurologic Manifestations

Manifestations at the level of the central nervous system, resulting in generalized anorexia and malaise or more severe disturbances such as ataxia, seizures, and coma, have been described in hypophosphatemia.[404,405,522] Neuromuscular abnormalities include paresthesias and weakness, the result of both myopathic changes and diminished nerve conduction.[72]

Skeletal Abnormalities

The skeletal abnormalities associated with hypophosphatemia, particularly in vitamin D–resistant rickets, may be quite marked. In addition, bony abnormalities, including osteomalacia and pathologic fractures, have been described in antacid-induced phosphate depletion,[37,139] as well as in hypophosphatemic patients undergoing hemodialysis who did not receive phosphate binding gels.[11] A rheumatic syndrome resembling ankylosing spondylitis also has been reported in hypophosphatemic patients.[464]

Gastrointestinal Disturbances

These manifestations include anorexia, nausea, and vomiting.[405] It has been speculated that hypophosphatemia in the alcoholic patient may further impair hepatic function through hypoxic insult.

Renal Manifestations

There is decreased phosphorus excretion and decreased tubular reabsorption of calcium, magnesium, bicarbonate, and glucose.[130,165,181,227,228,230] The renal conservation of phosphorus occurs early in the syndrome and is the result of a primary increase in the tubular reabsorption of the anion and a decrease in the GFR and consequently in the filtered load of phosphorus.[230,468] This mechanism results in complete renal conservation of phosphorus, with net losses representing only a small fraction of total body phosphorus stores.[405] The increase in phosphorus reabsorption seen with phosphorus depletion is independent of several hormones known to influence phosphorus transport under other circumstances, including PTH, vitamin D, calcitonin, and thyroxine.[640] The possibility that serum phosphorus concentration per se (or intracellular phosphorus) may in some manner regulate its absorption along the nephron seems plausible. Hypercalciuria of enough magnitude to produce a negative calcium balance is seen commonly in hypophosphatemic patients. Several factors contribute to this increase in calcium excretion including increased calcium mobilization from bone, enhanced GI tract calcium absorption, and inhibition of renal tubular calcium reabsorption.[130,165,181,227,228,230] These effects appear to be independent of PTH activity and may be the result of a direct effect of phosphate on these transport processes.

Acid–Base Disturbances

Renal bicarbonate wasting, diminished titratable acid excretion, and decreased ammoniagenesis have been reported in hypophosphatemia.[165,485] However, these defects are counterbalanced to some extent by the mobilization of alkali from bone. Thus, steady-state pH may be near normal at the expense of skeletal buffers.[181]

Differential Diagnosis of Hypophosphatemia

In general, the cause of hypophosphatemia can be determined either from the medical history or from the clinical setting in which it occurs. When the cause is in doubt, measurement of the urinary phosphorus excretion level may be helpful. If the urinary phosphorus concentration is less than 4 mg per dL when the serum phosphorus level is less than 2 mg per dL, renal losses may be excluded.[256] Of the three major extrarenal causes including diminished phosphorus intake, increased extrarenal losses (GI tract), and translocation into the intracellular space, the last is the most common, particularly in the hospitalized patient.[309,364]

When the urinary phosphorus excretion level is high, the differential diagnosis includes hyperparathyroidism, a primary renal tubular abnormality, or vitamin D–dependent or –resistant renal rickets. Measurements of serum calcium, PTH, and vitamin D and its metabolites, as well as urinary excretion of other solutes (glucose, amino acids, and bicarbonate), will usually elucidate the underlying disturbance that is responsible for the hypophosphatemia.

Treatment of Hypophosphatemia

There are several general principles that apply to the treatment of hypophosphatemic patients. As with any predominantly intracellular ion (e.g., potassium), the state of total body phosphorus stores, as well as the magnitude of phosphorus losses, cannot be readily assessed by measurement of the concentrations in serum. In fact, under conditions in which a rapid shift of phosphorus has resulted from glucose infusion or hyperalimentation, total body stores of phosphorus may be normal, although with diminished intake and renal losses, there may be severe phosphorus depletion. Furthermore, the volume of distribution of phosphorus may vary widely, reflecting in part the intensity and duration of the underlying cause.[364]

In clinical situations in which hypophosphatemia is to be expected (e.g., glucose infusion or hyperalimentation in the alcoholic or nutritionally compromised patient during treatment of diabetic ketoacidosis), careful monitoring of the concentration of serum phosphorus is crucial. In these situations, addition of phosphorus supplementation to prevent the development of severe hypophosphatemia may prove very helpful. Certainly, other contributing causes of hypophosphatemia in this setting should be identified and treated. This is particularly true of the use of phosphate binding antacids (aluminum and magnesium hydroxide) for peptic ulcer disease, which may be replaced by aluminum phosphate antacids (Phosphagel) or cimetidine (Tagamet). It is now generally recommended that hyperalimentation solutions contain a phosphorus concentration of 12 to 15 mmol per L or 37 to 46.5 mg per dL, in order to provide an appropriate amount of phosphorus in the patient in whom renal impairment is absent.[364] Phosphorus supplementation during glucose infusion or during the treatment of ketoacidosis is usually withheld until the serum phosphorus levels decrease to less than 1 mg per dL. Phosphorus may be given orally to these patients and others with mild asymptomatic hypophosphatemia in the form of skim milk, which contains 0.9 mg per mL, Neutra-phos (3.3 mg per mL), or phosphorus soda (129 mg per mL). However, intestinal absorption is quite variable, and diarrhea often complicates the oral administration of phosphate-containing compounds. For these reasons, parenteral administration is usually recommended in the hospitalized patient. If oral therapy is permissible, Fleet Phospho-Soda may be given at a dosage of 60 mmol daily in three doses (21 mmoL per 5 mL or 643 mg per 5 mL). A convenient method is to provide the phosphorus together with potassium replacement in these patients. Addition of 5 mL of potassium phosphate (K phosphate) into 1 L of intravenous fluid provides 22 mEq of potassium and 15 mmol (466 mg) of phosphorus.[364] However, because potassium losses may greatly exceed the phosphorus deficit, the repletion of potassium should not be totally linked to phosphorus therapy. In patients with severe phosphate depletion, it is difficult to determine the magnitude of the total deficit of phosphorus and to calculate a precise initial dose. It is usually prudent to proceed with caution and repair the deficit slowly. The most frequently recommended regimen is 0.08 mmol per kg of body weight (2.5 mg per kg body weight) given over 6 hours for severe but uncomplicated hypophosphatemia and 0.016 mmol per kg of body weight (5 mg per kg of body weight) in symptomatic patients.[364] Parenteral administration should be discontinued when the serum phosphorus concentration is greater than 2 mg per dL.

Calcium administration may be needed during phosphate repletion to prevent severe hypocalcemia. Calcium must not be added to bicarbonate- or phosphate-containing solutions because of the potential precipitation of calcium salts. Intravenous infusion of calcium gluconate or calcium chloride may be given until tetany abates. In addition to hypocalcemia, metastatic calcification, hypotension, hyperkalemia, and hypernatremia are potential side effects of parenteral infusion of phosphorus. These problems can be prevented by judicious use of therapy and frequent monitoring of serum electrolyte concentrations.

Hyperphosphatemia

Hyperphosphatemia is said to occur when the serum phosphorus concentration exceeds 4.6 mg per dL in adults. In children, serum levels of phosphorus of up to 6 mg per dL may be physiologic. The most frequent cause of hyperphosphatemia is decreased excretion of phosphorus in the urine as a result of a fall in the GFR. However, increases in serum phosphorus concentration can also occur as a result of increased entry into the ECF due to excessive intake of phosphorus, increased release of phosphorus from tissue breakdown, and release of phosphorus from the skeletal reservoir through bone resorption. The major causes of hyperphosphatemia are listed in Table 73.4.

Decreased Excretion of Phosphorus in Urine

Decreased Renal Function

In progressive kidney failure, phosphorus homeostasis is maintained by a progressive increase in phosphorus excretion per nephron.[624,625] As a result of increased phosphorus excretion per nephron, it is unusual to see marked hyperphosphatemia until GFRs decrease to less than 25 mL per minute.[624,625] Under physiologic conditions with a GFR of 120 mL per minute, a fractional excretion of 5% to 15% of the filtered load of phosphorus is adequate to maintain phosphorus homeostasis. However, as renal insufficiency progresses and the number of nephrons decreases, fractional excretion of phosphorus may increase to as high as 60% to

73.4 Causes of Hyperphosphatemia

I. Decreased renal excretion of phosphate
  A. Renal insufficiency
    1. Chronic
    2. Acute
  B. Hypoparathyroidism
  C. Pseudohypoparathyroidism
    1. Type I
    2. Type II
  D. Abnormal circulating parathyroid hormone
  E. Acromegaly
  F. Tumoral calcinosis
  G. Administration of bisphosphonates

II. Increased entrance of phosphorus into the extracellular fluid
  A. Neoplastic diseases
    1. Leukemia
    2. Lymphoma
  B. Increased catabolism
  C. Respiratory acidosis

III. Increased intake and gastrointestinal absorption of phosphorus
  A. Pharmacologic administration of vitamin D metabolites
  B. Ingestion and/or administration of phosphate salts

IV. Miscellaneous
  A. Cortical hyperostosis
  B. Intermittent hyperphosphatemia
  C. Artifacts

From Slatopolsky E. Pathophysiology of calcium, magnesium, and phosphorus. In: Klahr S, ed. The Kidney and Body Fluids in Health and Disease. New York: Plenum Press; 1983:269, with permission.

80% of the filtered load. This progressive phosphaturia per nephron serves to maintain the concentration of phosphorus within normal limits in plasma as renal disease progresses. The decrease in phosphate reabsorption per nephron is stimulated by increased PTH and FGF23 levels. However, when the number of nephrons is greatly diminished, if the dietary intake of phosphorus remains constant, phosphorus homeostasis can no longer be maintained and hyperphosphatemia develops. This usually occurs when the GFR falls to less than 25 mL per minute. As hyperphosphatemia develops the filtered load of phosphorus per nephron increases, phosphorus excretion rises, and phosphorus balance is reestablished but at higher concentrations of serum phosphorus, PTH, and FGF23. Hyperphosphatemia is a usual finding in patients with far-advanced renal insufficiency unless phosphorus intake in the diet has decreased through dietary manipulations or the patient is receiving phosphate binders such as calcium carbonate, sevelamer, or lanthanum carbonate that decrease the absorption of phosphate from the GI tract.[568] In patients with acute kidney injury (AKI), hyperphosphatemia is a common finding.[430] The degree of hyperphosphatemia in patients with acute renal failure varies considerably. It is quite marked in patients with renal insufficiency secondary to severe trauma or nontraumatic rhabdomyolysis.[335] Hyperphosphatemia in CKD and AKI directly stimulates osteocyte, osteoblast, odontoblast, and vascular smooth muscle cell signaling that results in gene transcription of RUNX2 and osterix.[434] In vascular smooth muscle cells of neointimal atherosclerotic plaques and cardiac valves, stimulation of RUNX2 and osterix produce matrix calcification akin to bone formation.[590] In mineralizing vascular smooth muscle cells, Pi is a signal stimulating molecule, and the sodium-dependent Pi transport protein PIT1 may be the phosphorus sensing receptor.[381] Thus, hyperphosphatemia is related to vascular calcification and both of these are cardiovascular risk factors in CKD.[69,398] Cardiovascular mortality is extremely high in CKD and hyperphosphatemia and vascular calcification account for much of this.[192,630]

Decreased or Absent Levels of Circulating Parathyroid Hormone

Hypoparathyroidism is characterized by low or absent levels of PTH, low levels of serum calcium, and hyperphosphatemia.[498] The most common causes of hypoparathyroidism result from injury to the parathyroid glands, or their blood supply during thyroid, parathyroid, or radical neck surgery. Idiopathic hypoparathyroidism is a rare disease. Because PTH normally inhibits the renal reabsorption of phosphorus, its absence leads to an elevation in the Tm for phosphorus and a decrease in the excretion of the anion in the urine. Balance is reestablished when the serum phosphorus concentration rises to 6 to 8 mg per dL. At this concentration of serum phosphorus, the filtered load of phosphate is increased, exceeding the Tm for phosphorus reabsorption, and a new steady-state is reestablished. Patients with hypoparathyroidism are easily diagnosed by the findings of a low level of serum calcium, hyperphosphatemia, and undetectable levels of circulating immunoreactive PTH. After several years of hypoparathyroidism, other signs may become manifest such as cataracts and bilateral symmetrical calcification of the basal ganglia on X-ray films of the skull. The most striking symptoms in patients presenting with hypoparathyroidism are related to an increase in neuromuscular excitability resulting from a decrease in the levels of ionized calcium in serum. Some patients may not develop hypocalcemia and severe tetany, but increased neuromuscular excitability may be demonstrated by contraction of facial muscles in response to stimulus over the facial nerve (Chvostek's sign) or by carpal spasm (Trousseau's sign) occurring 2 or 3 minutes after inflating a blood pressure cuff around the arm above systolic blood pressure. In other patients, psychiatric disturbances,

paresthesias, numbness, muscle cramps, and dysphagia may be presenting symptoms.

Pseudohypoparathyroidism

This is a relatively rare condition characterized by end-organ resistance to the action of PTH.[13] Characteristically, the kidney and skeleton do not respond appropriately to the action of PTH. Some patients with pseudohypoparathyroidism (PHP) may have specific somatic characteristics such as short stature, round face, short metacarpal bones and phalanges, and some degree of mental retardation. Biochemically, these patients, like those with hypoparathyroidism, have low concentrations of serum calcium and hyperphosphatemia. However, there are two important points in the differential diagnosis. First, in most patients with PHP, the circulating levels of immunoreactive PTH are elevated, whereas in patients with true hypoparathyroidism PTH levels are low or absent. Second, patients with PHP do not respond to the administration of exogenous PTH with phosphaturia. Patients with true hypoparathyroidism demonstrate a heightened phosphaturic response to administration of exogenous PTH. Two major types of PHP have been described. In type I, patients fail to increase the excretion of cAMP or phosphate in the urine in response to the administration of exogenous PTH. PHP type Ia is due to defects in the guanosine triphosphate (GTP) binding protein, $G_{S\alpha}$(the alpha subunit of the heterotrimeric stimulatory G protein), which is a product of the GNAS gene locus, whereas PHP type Ib is due to methylation defects in the imprinted GNAS cluster.[425] In other patients, there is an increase in cAMP in response to the administration of exogenous PTH but no phosphaturic response. This condition has been termed PHP type II.[169]

Abnormal Circulating Parathyroid Hormone

This syndrome is characterized by hyperphosphatemia, hypocalcemia, chronic tetany, and cataracts. These manifestations, as described previously, are those observed in patients with hypoparathyroidism, but these patients have normal or high serum levels of PTH. However, in contrast to patients with pseudohypoparathyroidism, they do respond to the exogenous administration of PTH, with an increase in the excretion of cAMP and phosphaturia. It has been postulated that the defect in these patients relates to an abnormal form of endogenous PTH that is devoid of physiologic effects.[137] However, this postulate has not been substantiated by characterization and analysis of the circulating PTH in these patients.

Acromegaly

GH decreases the urinary excretion of phosphorus and increases the Tm for phosphorus.[350] Hypersecretion of GH may lead to development of gigantism if the increased secretion occurs before the closure of the epiphysis or to acromegaly if the excessive secretion occurs after puberty. Hyperphosphatemia has been described in patients with acromegaly. It is known that serum phosphorus concentrations are higher in children (5 to 8 mg per dL) than in adults. This may be related in part to increased levels of circulating GH in children.

Tumoral Calcinosis

This condition, which is seen more frequently in young African Americans, is characterized by hyperphosphatemia, ectopic calcification around large joints, normal levels of circulating immunoreactive PTH, and a normal response to administration of exogenous PTH.[408,732] The extensive calcification of soft tissues observed in patients with this condition is most likely due to an elevated phosphorus–calcium product in blood. Despite the development of hyperphosphatemia, patients with tumoral calcinosis do not develop secondary hyperparathyroidism. This may be due to the fact that circulating levels of 1,25-dihydroxycholecalciferol remain within the normal range in these patients despite hyperphosphatemia. These normal levels of 1,25-dihydroxycholecalciferol maintain a normal GI tract absorption of calcium. This, combined with the decreased urinary calcium observed in these patients, may serve to maintain normal serum calcium values and prevent the development of secondary hyperparathyroidism.

The pathogenesis of this disease has been clarified by genetic studies of rare familial forms, see below. Mutations in three genes, FGF23, KLOTHO, and GALNT3, all related to FGF23 function, have been found to cause tumoral calcinosis.[48,291,667] Because acquired tumoral calcinosis is most often observed in association with kidney disease, which is characterized by reduced KLOTHO and FGF23 signaling, tumoral calcinosis is probably related to decreased phosphorus excretion by the kidney.[454]

Familial Tumoral Calcinosis

Familial tumoral calcinosis (FTC) is inherited in both autosomal recessive and autosomal dominant patterns.[407,409,410,455,495,521,629] The disease most commonly appears before the second decade of life, presenting as periarticular calcified masses of the hip, elbow, or shoulder. This disorder is associated with hyperphosphatemia and increased renal tubular Pi reabsorption, but with normal serum levels of calcium and parathyroid hormone. Serum levels of 1,25-dihydroxyvitamin D may be normal or elevated.

Biallelic mutations in the UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylglucosaminyltransferase 3 (GALNT3) gene have been identified in two large families as a cause of FTC.[290] GALNT3 encodes a glycosyltransferase responsible for initiating mucin-type O-glycosylation. FGF23 is O-glycosylated which blocks the recognition sequence for SPC and processing of FGF23. Thus, lack of GALNT3 function leads to reduced FGF23 levels. Furthermore, inactivating mutations of FGF23 have been shown to cause tumoral calcinosis.[48] Recently, mutations in the KLOTHO gene have also been shown to cause familial tumoral calcinosis.[291] Thus, familial tumoral calcinosis is a disease of decreased FGF23 signaling.

Administration of Bisphosphonates

Administration of bisphosphonates, which are used in the treatment of Paget disease and osteoporosis, may result in the development of hyperphosphatemia.[685] The mechanisms by which bisphosphonates increase serum phosphorus are not completely clear but may involve an alteration in phosphate distribution between different cellular compartments and a decrease in renal phosphorus excretion. It appears that the levels of both circulating PTH and the urinary excretion of cAMP after administration of exogenous PTH are within the normal range in patients receiving bisphosphonates.

Redistribution of Phosphorus between Intracellular and Extracellular Pools

Tumor Lysis Syndrome

Various syndromes of tissue breakdown may result in the development of hyperphosphatemia and subsequent hypocalcemia. Hyperphosphatemia has been described in patients with several types of lymphomas. Patients receiving treatment for lymphoblastic leukemia may develop hyperphosphatemia with a concomitant decrease in serum calcium concentration.[734] The phosphorus load originates primarily from the destruction of lymphoblasts, which have about four times the concentration of organic and inorganic phosphorus present in mature lymphocytes.

Similar findings have been described during treatment of Burkitt lymphoma. Cohen et al.[133] reviewed the acute tumor lysis syndrome associated with the treatment of Burkitt lymphoma. In 37 patients with American Burkitt lymphoma, azotemia occurred in 14 patients and preceded chemotherapy in eight. Pretreatment of azotemia was associated with elevated levels of lactate dehydrogenase (LDH) and uric acid and sometimes extrinsic ureteral obstruction by the tumor. After chemotherapy, major metabolic complications related to tumor lysis were associated with large tumors and high LDH levels and were manifested by hyperkalemia, hyperphosphatemia, and hyperuricemia. Elevated phosphorus levels were seen in 31% of nonazotemic patients and in all azotemic patients. Hemodialysis was required in three patients for control of azotemia, hyperuricemia, hyperphosphatemia, or hyperkalemia.

Tsokos et al.[669] studied the renal metabolic complications of other undifferentiated lymphomas and lymphoblastic lymphomas. These workers found that serum LDH concentration before chemotherapy correlated well with the stage of disease and predicted the serum levels of creatinine, uric acid, and phosphorus in the posttreatment period. Patients with LDH values of more than 2,000 IU were likely to develop severe hyperphosphatemia. When azotemia developed in the postchemotherapy period, it was attributed to hyperuricemia or hyperphosphatemia. Some of these patients had elevated serum phosphorus levels in the range of 20 to 30 mg per dL, which may contribute to the development of renal insufficiency due to calcium deposition in the kidney and other tissues.

Thus, there is a great risk of hyperphosphatemia in patients undergoing chemotherapy for rapidly growing malignant lymphomas. The best method of prevention of this complication, as well as the best therapeutic intervention, has not been well defined. Initially, it appears useful to attempt to increase the renal excretion of phosphate during the induction of remission by chemotherapy in these patients. This requires infusion of large amounts of saline and possibly bicarbonate, which has been shown to increase renal phosphorus excretion above and beyond the mere effects of volume expansion. Acetazolamide, a potent phosphaturic agent, might also be beneficial in these individuals. The general recommendation of hemodialysis as the prime therapeutic modality for hyperphosphatemia and acute renal insufficiency resulting from tumor lysis is not based on experimental data. Although hemodialysis no doubt rapidly lowers serum phosphorus levels, the mass of phosphorus continually presented to the extracellular space from ongoing tissue breakdown is not continuously treated by this modality. Thus, it is possible that combined hemodialysis and peritoneal dialysis, or even peritoneal dialysis alone, might be as, if not more, beneficial and safer in individuals with tumor lysis syndrome.

Increased Catabolism

Conditions characterized by increased protein breakdown (e.g., severe tissue muscle damage and severe infections) may sometimes be accompanied by hyperphosphatemia. Although the hyperphosphatemia may be related simply to translocation of phosphorus into the extracellular space, other factors seem to play a role. Hyperphosphatemia has been described in patients with ketoacidosis before treatment. After administration of intravenous fluids and insulin therapy, the entrance of glucose into the cells is usually followed by movement of phosphorus back into the intracellular space, and some patients now may develop hypophosphatemia. Thus, the combination of dehydration, acidosis, and tissue breakdown in different catabolic states may lead to hyperphosphatemia.

Respiratory Acidosis

Acute respiratory acidosis may lead to a marked increase in serum phosphorus concentration.[217] By contrast, chronic respiratory acidosis is usually not manifested by sustained elevated levels of serum phosphorus. Acute rises in P_{CO_2} in experimental animals have been shown to lead to increased serum phosphorus levels. The modest degree of hyperphosphatemia seen in chronic respiratory acidosis is probably related to renal compensation and increased phosphorus excretion via the kidney to maintain phosphorus homeostasis.

Increased Intake and Gastrointestinal Absorption of Phosphorus

Administration of Phosphate Salts or Vitamin D or Its Metabolites

Administration of vitamin D_3 or its metabolites, particularly 1,25-dihydroxycholecalciferol, may result in increases in serum phosphorus, particularly in uremic patients. These

compounds very likely may result in hyperphosphatemia in uremic individuals by increasing phosphorus absorption from the gut and perhaps by potentiating the effect of PTH on the skeleton with increased release of phosphorus from bone. Decreased renal function limits the compensatory mechanism of the kidney to excrete the increased load of phosphate entering the extracellular space. In addition to elevating serum phosphorus levels, vitamin D metabolites may result in hypercalcemia. An increase in the phosphorus–calcium product may result in tissue deposition of calcium, particularly in the kidney, leading to further renal functional deterioration.

Ingestion or Administration of Salts Containing Phosphate

Hyperphosphatemia has been observed in adults ingesting laxative-containing phosphate salts or after administration of enemas containing large amounts of phosphate.[273,441] Intravenous phosphate administration has been used in the treatment of hypercalcemia of malignancy. The administration of 1 to 2 g of phosphate intravenously decreases the concentration of serum calcium. Unfortunately, the severe hyperphosphatemia induced by administration of large amounts of phosphorus intravenously may lead to calcium-phosphate precipitation in important organs such as the heart and kidney, and several deaths resulting from this form of therapy have been reported. Hyperphosphatemia may develop in newborn infants who are fed cow's milk, which is higher in phosphorus content than human milk. This may be an important factor in the genesis of neonatal tetany.

Clinical Manifestations of Hyperphosphatemia

Acute hyperphosphatemia following administration of phosphate enemas or oral sodium phosphate solution has been associated with acute and chronic renal failure or acute phosphate nephropathy.[5,426] Otherwise, most of the clinical effects of hyperphosphatemia are related to secondary changes of calcium metabolism. Hyperphosphatemia produces hypocalcemia by several mechanisms (Fig. 73.7), including decreased production of 1,25-dihydroxycholecalciferol, precipitation of calcium, and decreased absorption of calcium from the gastrointestinal tract, presumably due to a direct effect of phosphorus on calcium absorption.[462] In addition to the manifestations by hypocalcemia, which are described elsewhere in this chapter, ectopic calcification is one of the important manifestations of hyperphosphatemia. The association of hyperphosphatemia and ectopic calcification has been observed in several clinical settings including in patients with chronic renal failure, hypoparathyroidism, and tumoral calcinosis. It appears that when the calcium–phosphorus product exceeds 70, the likelihood for calcium precipitation is greatly increased. In addition to the calcium–phosphorus product, local tissue factors may play an important role in calcium deposition. For example, regional changes in pH (local alkalosis) may favor

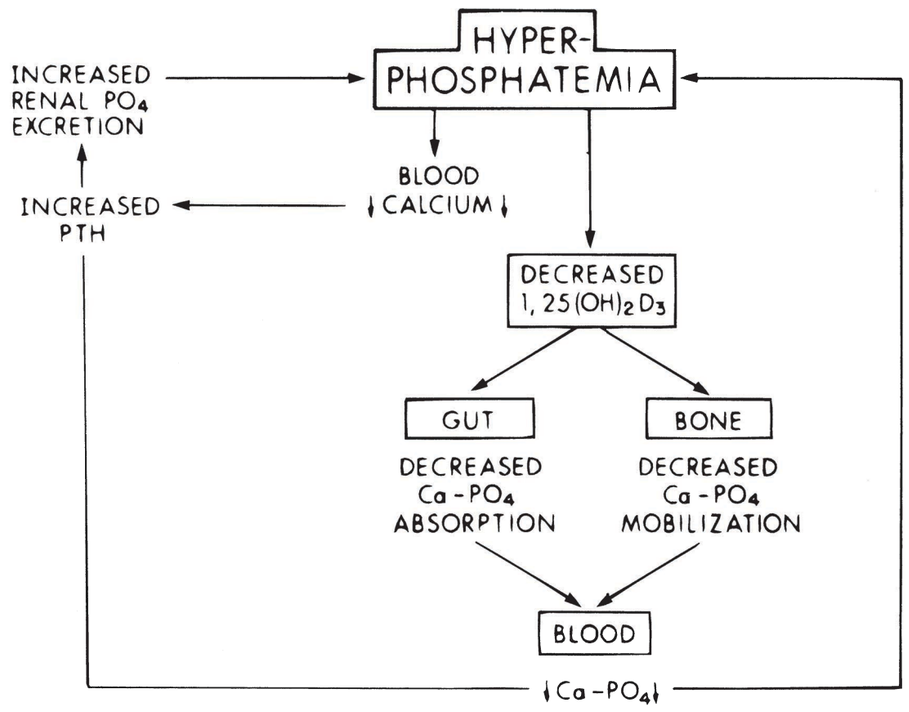


FIGURE 73.7 Pathophysiologic changes occurring during the development of hyperphosphatemia. These changes tend to increase the urinary excretion of phosphorus and to correct the hyperphosphatemia.

calcification in tissue such as cornea and lungs. In patients with severe calcification (calciphylaxis), it appears that high levels of circulating PTH may also aggravate this condition. Hyperphosphatemia plays a key role in the development of secondary hyperparathyroidism in patients with renal insufficiency. It has been observed that when phosphate ingestion is decreased and hyperphosphatemia is prevented in experimental animals with induced renal insufficiency, hyperparathyroidism can be prevented.[622] The mechanisms presumably relate to maintenance of serum calcium levels with prevention of hyperphosphatemia and, at the same time, continued synthesis of 1,25-dihydroxycholecalciferol, the circulating levels of which may directly influence the secretion of PTH.[229,628] Several investigators[156,499,611,623] have demonstrated that dietary phosphate markedly influences the rate of parathyroid cell proliferation and PTH synthesis and secretion independent of changes in ionized calcium or 1,25-dihydroxycholecalciferol. It seems that the mechanism by which phosphorus increases PTH synthesis and secretion is posttranscriptional. Moreover, in experimental uremic rats, it has been shown that phosphate restriction suppresses parathyroid cell growth by inducing p21, a repressor of the cell cycle. On the other hand, a high phosphate intake rapidly (3 to 5 days) induces significant parathyroid cell hyperplasia by inducing an increase in transforming growth factor α (TGFα).[344] TGFα, which is known to promote growth not only in malignant transformation but also in normal tissues,[170,176] is enhanced in hyperplastic and adenomatous human parathyroid glands.[226] In patients on chronic hemodialysis, the degree of hyperparathyroidism correlates well with the concentration of serum phosphorus. Patients who do not adhere to their therapeutic prescriptions requiring ingestion of phosphate binders seem to develop more severe and persistent hyperphosphatemia with marked secondary hyperparathyroidism and bone disease than patients who adhere carefully to dietary and therapeutic prescriptions.

Vascular calcification has been observed in some patients with chronic renal insufficiency and severe calcification, hyperphosphatemia, and hyperparathyroidism, leading to necrosis and gangrene of extremities. Slit-lamp examination may show ocular calcification, and some patients may develop acute conjunctivitis, the so-called red eye syndrome of uremia. Precipitation of calcium in the skin may be in part responsible for pruritus, a symptom that is usually seen in patients with far-advanced uremia. It has been reported that parathyroidectomy in such patients may alleviate the symptoms. From the therapeutic point of view, the most efficacious way of controlling hyperphosphatemia is through the use of phosphate binders that decrease the absorption of phosphorus from the GI tract. In patients with adequate renal function, expansion of the ECF with saline will greatly increase phosphorus excretion in the urine and contribute to correction of the hyperphosphatemia.

Treatment of Hyperphosphatemia

Decreased absorption of phosphate from the GI tract is a cornerstone of treatment of hyperphosphatemia. Phosphate absorption from the GI tract can be markedly decreased by decreasing the amount of phosphorus in the diet, by administering phosphate binding agents capable of decreasing absorption of phosphorus, or both. Because protein requirements limit the amount of phosphorus restriction that can be achieved through dietary manipulation, from a practical point of view, administration of agents capable of decreasing phosphorus absorption from the GI tract is the mainstay of treatment. Administration of calcium salts has replaced aluminum salts as the traditional treatment to control hyperphosphatemia. Most of these preparations require the administration of two to four tablets or capsules three or four times daily. If the patient develops constipation, one of the complications of such medications, magnesium salts may be incorporated into these preparations. However, if the patient has hyperphosphatemia secondary to severe renal insufficiency, magnesium should not be given because of the likelihood of producing severe hypermagnesemia, which may lead to magnesium intoxication, muscle paralysis, and death.

The elucidation of aluminum toxicity, which results from prolonged administration of aluminum-containing salts, as phosphate binders to patients with chronic renal insufficiency, has led to diminished use of these agents or their elimination.[52,689] Several studies indicate that calcium carbonate[463,626,627] is an effective agent for control of hyperphosphatemia in chronic renal failure. However, numerous investigators have demonstrated an increase in the number of aortic and mitral valve calcifications in patients on dialysis when compared with the general population. Cardiovascular events are responsible for a 40% to 60% mortality rate of patients on dialysis.[240,397,547,558] Morbidity and mortality rates increase as the $Ca–PO_4$ product raises to more than 60. Braun et al.,[88] with the use of electron beam computed tomography (CT), demonstrated a significant deposition of calcium in the coronary arteries of patients on dialysis. Although coronary artery calcifications worsen with age, this abnormality has been demonstrated in young patients.[231] In fact, postmortem examination of children with renal failure demonstrated that 60% to 70% had calcification of the heart, lungs, and blood vessels.[452] Positive calcium balances of 500 to 900 mg daily were demonstrated in uremic patients receiving large doses of calcium carbonate.[627] Thus, it is critical not only to reduce the $Ca–PO_4$ product to less than 60, but also to significantly decrease the calcium load that patients receive to control serum phosphorus.

To avoid these deleterious side effects, well-tolerated calcium albumin–free phosphate binders have been developed—sevelamer hydrochloride or carbonate and lanthanum carbonate that are not absorbed from the GI tract that interact with phosphate ions. Several short-term clinical studies in patients with end-stage renal disease (ESRD) have established that they are effective phosphate binders without increasing the calcium load to the patients.[121,621] In addition, sevelamer hydrochloride decreases low-density lipoprotein cholesterol by 30% to 40%, and in long-term studies increases high-density lipoprotein cholesterol by 20% to 30%; it does not affect triglycerides.[122]

Studies have shown that nicotinamide may also be an effective agent to decrease serum phosphorus levels. Because nicotinamide is an inhibitor of sodium-dependent phosphate cotransport in rat renal tubule and small intestine,[315,719] studies have examined whether nicotinamide reduces serum levels of phosphorus and intact parathyroid hormone (iPTH) in patients undergoing hemodialysis. Sixty-five hemodialysis patients with a serum phosphorus level of more than 6.0 mg per dL after a 2-week washout of calcium carbonate were enrolled in this study. Nicotinamide was administered for 12 weeks. The starting dose was 500 mg per day, and the dose was increased by 250 mg per day every 2 weeks until serum phosphorus levels were well controlled at less than 6.0 mg per dL. A 2-week posttreatment washout period followed the cessation of nicotinamide. Blood samples were collected every week for measurement of serum calcium, phosphorus, lipids, iPTH, and blood nicotinamide adenine dinucleotide (NAD). The mean dose of nicotinamide was 1080 mg per day. The mean blood NAD concentration increased from 9.3 ± 1.9 nmol per 105 erythrocytes before treatment to 13.2 ± 5.3 nmol per 105 erythrocytes after treatment. The serum phosphorus concentration increased from 5.4 ± 1.5 mg per dL to 6.9 ± 1.5 mg per dL with the pretreatment washout, then decreased to 5.4 ± 1.3 mg per dL after the 12-week nicotinamide treatment, and rose again to 6.7 ± 1.6 mg per dL after the posttreatment washout. Serum calcium levels decreased during the pretreatment washout from 9.1 ± 0.8 mg per dL to 8.7 ± 0.7 mg per dL with the cessation of calcium carbonate. No significant changes in serum calcium levels were observed during nicotinamide treatment. Median serum iPTH levels increased with pretreatment washout from 130.0 (32.8 to 394.0) pg per mL to 200.0 (92.5 to 535.0) pg per mL and then decreased from the maximum 230.0

(90.8 to 582.0) pg per mL to 150.0 (57.6 to 518.0) pg per mL after the 12-week nicotinamide treatment. With nicotinamide, serum high-density lipoprotein (HDL) cholesterol concentrations increased from 47.4 ± 14.9 mg per dL to 67.2 ± 22.3 mg per dL and serum low-density lipoprotein (LDL) cholesterol concentrations decreased from 78.9 ± 18.8 mg per dL to 70.1 ± 25.3 mg per dL; serum triglyceride levels did not change significantly.[654] This study demonstrated that nicotinamide may provide an alternative for controlling hyperphosphatemia and hyperparathyroidism without inducing hypercalcemia in hemodialysis patients.

Although decreased GI absorption of phosphorus is an effective way to control hyperphosphatemia in patients with renal insufficiency, excretion of phosphorus through the kidney is also an important mechanism. Thus expansion of the ECF volume may markedly increase phosphorus excretion by the kidney. This result is presumably related both to direct effects of volume expansion on the kidney, which decreases salt and water reabsorption and hence phosphorus reabsorption, and to increased PTH release, particularly as a consequence of decreased ionized calcium during volume expansion. In patients with marked renal insufficiency or with marked degrees of hyperphosphatemia due to tumor lysis or chemotherapy, peritoneal dialysis or hemodialysis may be used to remove large quantities of phosphorus from the extracellular space. Redistribution of phosphorus from the intracellular to the extracellular space can sometimes be rapidly corrected by the administration of glucose and insulin. In general, mild degrees of hyperphosphatemia can be tolerated, particularly if calcium levels are not markedly elevated. The goal in patients with chronic renal insufficiency is to keep phosphorus levels at less than 4.5 mg per dL to avoid falls in serum ionized calcium and marked development of severe hyperparathyroidism.

CALCIUM

Calcium, the most abundant cation of the body and the principal mineral of the human skeleton, is essential to the integrity and function of cell membranes, neuromuscular excitability, transmission of nerve impulses, multiple enzymatic reactions, and regulation of hormones such as PTH, calcitonin, and 1,25-dihydroxycholecalciferol. A complex homeostatic system involving the interplay of the bones, the kidneys, and the intestine has evolved to maintain calcium concentrations within a narrow range.

Distribution of Calcium

The total amount of calcium in the human body ranges from 1,000 to 1,200 g or 20 to 25 g per kg of fat-free body tissue. Approximately 99% of body calcium resides in the skeleton; the other 1% is present in the extracellular and intracellular spaces. About 1% of the calcium in the skeleton is freely exchangeable with calcium in the ECF. Together, these two fractions are known as the exchangeable pool of calcium and account for 2% of total body calcium. Calcium in bone is primarily crystalline hydroxyapatite, although some calcium exists as amorphous crystals in combination with phosphate. The normal calcium:phosphate ratio in bone is 1.5:1.

Extracellular Calcium

In humans, the serum calcium concentration is kept remarkably constant, between 9.0 and 10.4 mg per dL, or 4.5 to 5.2 mEq per L, or 2.25 to 2.6 mmol per L. About 50% of serum calcium is ionized and 10% is complexed with citrate, phosphate, bicarbonate, and lactate. These two fractions, ionized plus complexed calcium (ultrafiltrable calcium), make up approximately 60% of the total serum calcium. The rest, 40%, is protein bound, mainly to albumin. In hypoproteinemic states, such as the nephrotic syndrome or cirrhosis, although total serum calcium may be low, the ionized fraction may be within the normal range. Five to 10% of the calcium is bound to globulins. It is unusual for total serum calcium concentrations to change because of alterations in the levels of serum globulins. However, in severe hyperglobulinemia, such as may occur in patients with multiple myeloma or other dysproteinemias, elevations of total serum calcium concentrations may be observed.

Intracellular Calcium

Calcium is the major intracellular ionic messenger for the activation of many biologic processes.[286] The intracellular concentration of calcium is approximately 0.15 μM (Table 73.5 and Fig. 73.8). Cells extrude calcium via pumps or exchangers, sequester it in intracellular organelles, or use low-affinity binding sites with large capacities to maintain free calcium, Ca^{2+}, at the 0.15 μM level.[109,303] Intracellular calcium is complexed with ions such as orthophosphate or pyrophosphate and is bound to organic molecules such as ATP and proteins. Three major cellular calcium pools exist: (1) bound to multiple diverse sites, (2) sequestered in intracellular organelles, and (3) bound or free within the cytosol.[286]

Extrusion of Ca^{2+} from the cell and sequestration in intracellular organelles are transport functions generally carried out by two mechanisms, Na^{+}-Ca^{2+} exchange and Ca-ATPase (Table 73.5 and Fig. 73.8).[109,166,303,416,481,577,714] In cardiac muscle, nerve, brain, and kidney, calcium extrusion is directly coupled to sodium transport.[481,545] The Na^{+}-Ca^{2+} transport system depends on the asymmetric distribution of Na^{+} across the plasma membrane. The Na-K-ATPase of the plasma membrane maintains the Na^{+} gradient. Thus, the movement of Na^{+} into the cell is coupled to the flux of Ca^{2+} out of the cell. This Na^{+}-Ca^{2+} antiport system is electrogenic with a stoichiometry of three Na^{+} per Ca^{2+}.[111,545] A second and more ubiquitous mechanism of calcium efflux energizes uphill transport of calcium by the hydrolysis of high-energy–yielding phosphate bonds of ATP.[416,577,639]

The cytosolic calcium concentration is also maintained by an active transport into mitochondria and the endoplasmic reticulum (Fig. 73.8). It has been shown that mitochondria accumulate Ca^{2+} through a Ca-uniporter, with Ca^{2+} moving down an electrochemical gradient. The K_m for

73.5 Epithelial Calcium Transporters

Plasma membrane
- A. Calcium channels
  1. TRPV5
  2. TRPV6
- B. Calcium buffer proteins
  1. Calbindin −9K
  2. Calbindin −28K
- C. Calcium/Na exchangers
  1. NCX1
  2. NCX2
  3. NCX3
- D. Calcium ATPases
  1. PCA1
  2. PMCA2
  3. PMCA3
  4. PMCA4

Endoplasmic reticulum/Golgi
- A. Calcium ATPase
  1. SERCA: IP_3 sensitive Ca release channel

Mitochondria
- A. Calcium channel (uniporter)

Ca^{2+} of the uniporter is about 1 μmmol per L. Mitochondria also contain an Na^{+}-Ca^{2+} exchange mechanism. In the mitochondria, calcium and phosphate ions form insoluble amorphous tricalcium phosphate, a reaction that releases hydrogen ions into the cytosol. Cell injury may lead to a rise in intracellular calcium sufficient for Ca^{2+} to be sequestered in the mitochondria.[168] Ca^{2+} is sequestered in the endoplasmic reticulum by the action of a Ca-ATPase, which differs in properties from that found on the plasma membrane and Golgi apparatus.[343,466] During the early response of cells to certain stimuli, production of IP_3 and cyclic adenosine diphosphate ribose stimulates the opening of Ca^{2+} channels in the endoplasmic reticulum, serving to transiently increase cytosolic Ca^{2+} and allow the ion to act as an intracellular signal. Recently, polycystin-2 has been identified as an IP_3 sensitive ER Ca release channel.[339] Polycystin-2 is the product of the gene mutated in type 2 autosomal dominant polycystic kidney disease (ADPKD).[339] This identifies polycystin-2 as a critical regulator of renal tubular epithelial cell Ca signaling, and suggests that disordered Ca signaling during development leads to polycystic kidney disease.

Skeletal Calcium

More than 99% of the total body calcium is found in the skeleton. Bone consists of approximately 40% mineral, 30% organic matrix, and 30% water. Bone mineral exists

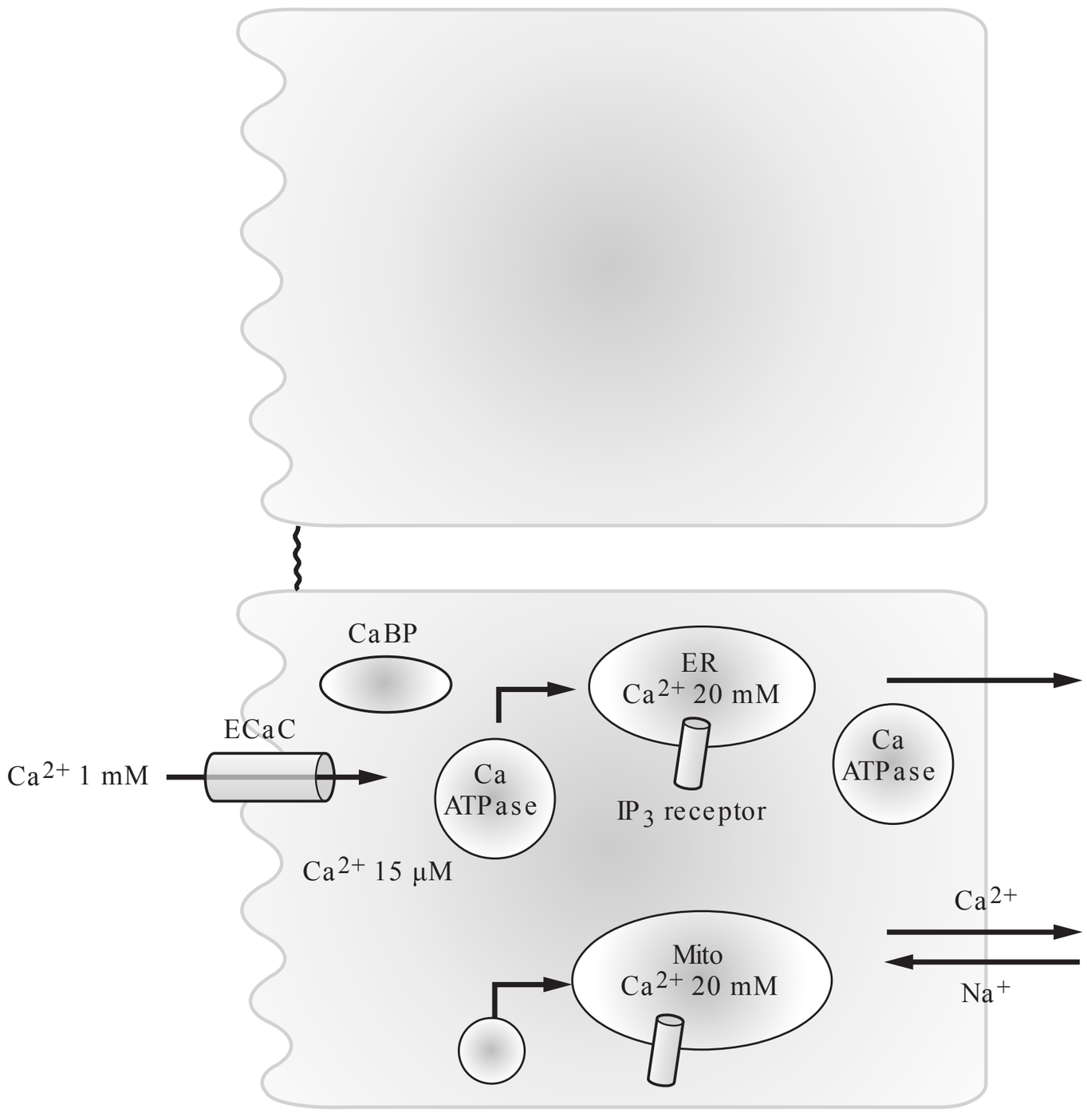


FIGURE 73.8 Control of intracellular calcium. The distal tubule epithelial cell is portrayed as an example of cellular control of cytosolic Ca^{2+} concentrations. Cells extrude Ca by energy (ATP) dependent pumps to maintain cytosolic levels at the 0.15 μM range. Intracellular stores in the endoplasmic reticulum (ER) and the mitochondria (Mito) have pumps to load in Ca and release channels, the IP_3 receptor, and the ryanodine receptor for the ER. Entry of calcium is controlled by entry channels, TRPV5 (which was originally called ECaC) in the case of the distal tubule epithelium and Na/Ca exchange transporters. Ca entering the cell is sequestered by vesicles enriched in calbindin 8K (CaBP) or 25K in the kidney and intestine, respectively.

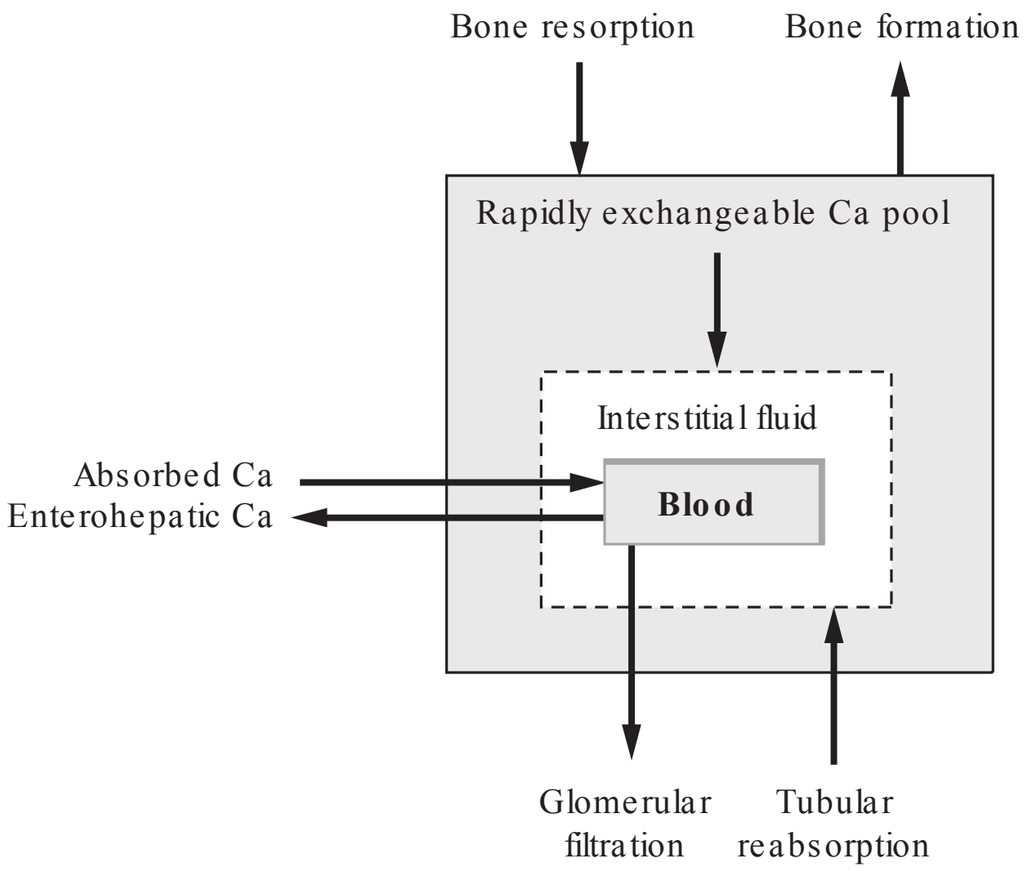


FIGURE 73.9 The exchangeable Ca pool. Absorbed Ca from the intestine enters the interstitial fluid and blood compartments. These compartments are in equilibrium with a larger complexed Ca compartment located in the mineralization fronts at sites of skeletal remodeling and bone formation. Ca leaves the exchangeable pool by the enterohepatic circulation, glomerular filtration, and bone formation. Besides intestinal absorption, Ca enters the exchangeable pool by bone resorption and tubular reabsorption.

in two physical forms, the amorphous and the crystalline. The amorphous form consists mainly of brushite and tricalcium phosphate; the crystalline form is composed mainly of hydroxyapatite. More than 90% of the organic material of the bone matrix is in the form of collagen fibers that are arranged in bundles with specific interaction with hydroxyapatite. Crystalline skeletal Ca is the huge Ca depot that is slowly exchangeable with blood and interstitial fluid pools of extracellular Ca. A large rapidly exchangeable Ca pool is also found in the skeleton (Fig. 73.9). The nature of the freely exchangeable calcium pool in bone is unknown, but it is unlikely to be collagen-associated hydroxyapatite. The Ca pool is likely amorphous and found associated with areas of active bone formation (mineralization fronts) where Ca is being deposited into the crystalline (poorly exchangeable) pool of bone.

A coupled process of bone resorption and formation (remodeling) is responsible for exit of calcium from the exchangeable pool (bone formation) and release of skeletal calcium (bone resorption) into the exchangeable pool. Remodeling imbalance contributes to serum calcium in certain disease states, especially CKD. Pathologic states in which bone resorption is increased (i.e., when bone resorption is greater than bone formation) produce profound changes in calcium homeostasis. In states wherein bone formation is decreased and bone resorption continues in excess (i.e., the renal adynamic bone disorder), hypercalcemia is often observed.[347] Bone remodeling is a coupled process because the activation of a remodeling unit sets two cell differentiation programs into operation—that of the osteoblast and that of the osteoclast. Bone marrow stromal cells, the osteoprogenitors that will become osteoblasts, harbor the receptors that are recognized by the factors capable of activating bone remodeling. Their stimulation results in the synthesis of a cell-attached ligand for RANK (receptor for activation of nuclear factor kappa B) on osteoclast progenitors, known as RANK ligand (RANKL).[102,336,349] RANKL and macrophage colony-stimulating factor (MCSF-1) are the critical osteoclast differentiation factors, and these local bone marrow factors are sufficient to direct osteoclast formation. Thus, stimulation of osteoblastic cells leads to stimulation of osteoclasts, and the process of skeletal remodeling represents bone formation and bone resorption.

The osteoclasts responsible for bone resorption are multinucleated giant cells lying in irregular indentations of the bone surface known as Howship's lacunae. Bone resorption depends on the number and activity of osteoclasts. The process of bone resorption performed by the osteoclasts includes the production of an acidic environment by proton secretion and matrix degradation by cathepsin K. The osteoblasts, on the other hand, are the cells responsible for the repair process after bone resorption (bone formation). Differentiation of the cells in the osteoblast lineage begins with specification of mesenchymal stem cells to the lineage by expression of osteoblast-specific transcription factors—RUNX2[172] and Osterix.[476] RUNX2 expression is stimulated by the bone morphogenetic protein subfamily of the TGFβ superfamily responsible for the direction of osteoblast differentiation and bone formation. Cells early in the process of osteoblast differentiation initiate bone matrix production by the biosynthesis of collagen. Thereafter, the matrix is mineralized by the deposition of calcium and phosphate, with formation of amorphous material initially and then development of hydroxyapatite. The deposition of mineral occurs along a well-defined front ("mineralization front"), outside of which there is an osteoid border or seam. The osteoid begins to calcify about 10 days after deposition. From the architectural point of view, the skeleton is composed of two types of bone: (1) compact cortical bone, which surrounds the marrow cavity and forms the shaft of the long bones, and (2) cancellous or trabecular bone, which is the main component of flat bones, such as ribs, and vertebra.

A differentiation between two other general types of bone is critical in the diagnosis of metabolic bone disease. The first, called woven bone (immature bone)[1] is a loosely organized, highly mineralized bone in which the collagen fibers are coarsely arranged and the osteocytes are large and irregular in size and shape. Woven bone is formed by simultaneous and unorganized actions of many cells. The calcification of the tissue is patchy, occurring in a speckled pattern and independent of the presence of vitamin D activity. Woven bone is present in the fetus, but after age 14 is no longer found in the human skeleton, except with pathologic

conditions such as chronic kidney disease, Paget disease, hyperparathyroidism and during rapid bone turnover, as in the presence of healing fractures.[1,2,670] The second general type of bone is lamellar bone (mature bone), which is the major component of the normal adult skeleton. It is a highly organized tissue in which the collagen bundles are arranged in successive layers, between which are cells called osteocytes. Lamellar bone is the product of synchronized activity by the osteoblast depositing collagen materials at a specific cell surface.

Another difference between woven bone and lamellar bone relates to the relation of mineral to collagen. In lamellar bone, the relative amounts of collagen and minerals are closely related, making hypermineralization in these bones difficult. Mineralization of woven bone is disorderly, and the degree of mineralization varies enormously; thus, hypermineralization (osteosclerosis) may occur in this type of bone.[1,2,86]

PTH, in conjunction with PTH-related peptide (PTHrP), other locally produced cytokines, and vitamin D, play key roles in bone turnover. At physiologic doses, PTH has an anabolic effect, increasing bone formation. Thus, PTH, by increasing calcium reabsorption by the kidney and gut and through stimulation of the osteoblast, affects the rate of bone formation. However, in pathologic conditions (e.g., hyperparathyroidism), the concentration of PTH in serum may be increased 10- to 50-fold. At this high concentration, PTH increases the activity and number of osteoclasts; thus, bone resorption predominates over bone formation, and minerals and organic matrix are removed from bone and enter the ECF. Not only PTH but also other hormones such as PTH-related proteins, thyroxine, interleukin-1 (IL-1), and tumor necrosis factor can produce severe hypercalcemia by increasing the activity of osteoclasts. The bone remodeling in these conditions, such as renal failure, is characterized by increased woven bone.[86,280,421]

Calcium Balance

Approximately 700 to 2,000 mg of Ca is ingested daily in the diet. However, this amount may vary depending on the amount of milk consumed. Milk and cheese are the major sources of Ca, contributing 50% to 70% of the total amount ingested in the diet. In the United States, 1 L of milk contains approximately 800 to 900 mg of Ca. About 10 to 15 mg of Ca per kilogram of body weight is the recommended daily intake. Ca needs may vary widely; for instance during the last trimester of pregnancy, there is an increased requirement for Ca because approximately 20 to 30 g of Ca enters the fetus. Transfer of Ca from the mother to milk during lactation is another instance of increased Ca demand.[675] In these states, intestinal absorption may not be sufficient and regulation of extracellular Ca by the calcium sensor, PTH and PTHrP, regulate the intestine and the skeleton to supply the needed Ca. With age, active intestinal Ca absorption declines; thus, an increase in Ca intake may be necessary to maintain Ca homeostasis. When 1 g of Ca is ingested in the diet, approximately 800 mg is excreted in the feces and 200 mg in the urine (Fig. 73.10). With a normal Ca intake (700 to 1,000 mg per day), approximately 30% to 40% of ingested Ca is absorbed in the intestine. However, on lower Ca diets, the percentage of Ca absorbed increases, and the percentage of Ca absorbed decreases when the diet has a high Ca content (more than 1,500 mg per day). The mechanisms responsible for this adaptation have been partially characterized and require the participation of PTH, vitamin D, and perhaps calcitonin. With low-Ca diet feeding, mild hypocalcemia activates the parathyroid gland chief cell Ca sensor and the release of PTH, which increases the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol in the renal cortex. 1,25-Dihydroxycholecalciferol is the hormonal metabolite of vitamin D, and it increases the intestinal absorption of Ca and mobilizes Ca from bone, synergistically with PTH. Thus, serum Ca levels return to normal. On the other hand, if the patient is fed a high-Ca diet, the mild hypercalcemia inhibits the chief cell Ca sensor, suppressing PTH, and stimulates the release of calcitonin from the C cells of the thyroid. In the absence of PTH, the activity of the 1α-hydroxylase is diminished and the 24-hydroxylase is activated; thus, the kidney makes preferentially 24,25-dihydroxycholecalciferol [$24,25(OH)_2D_3$], which is less efficient than 1,25-dihydroxycholecalciferol in promoting Ca absorption from the GI tract and mobilizing calcium from the skeleton. Fecal calcium consists of the fraction of ingested Ca that is not absorbed plus 100 to 200 mg of Ca secreted by

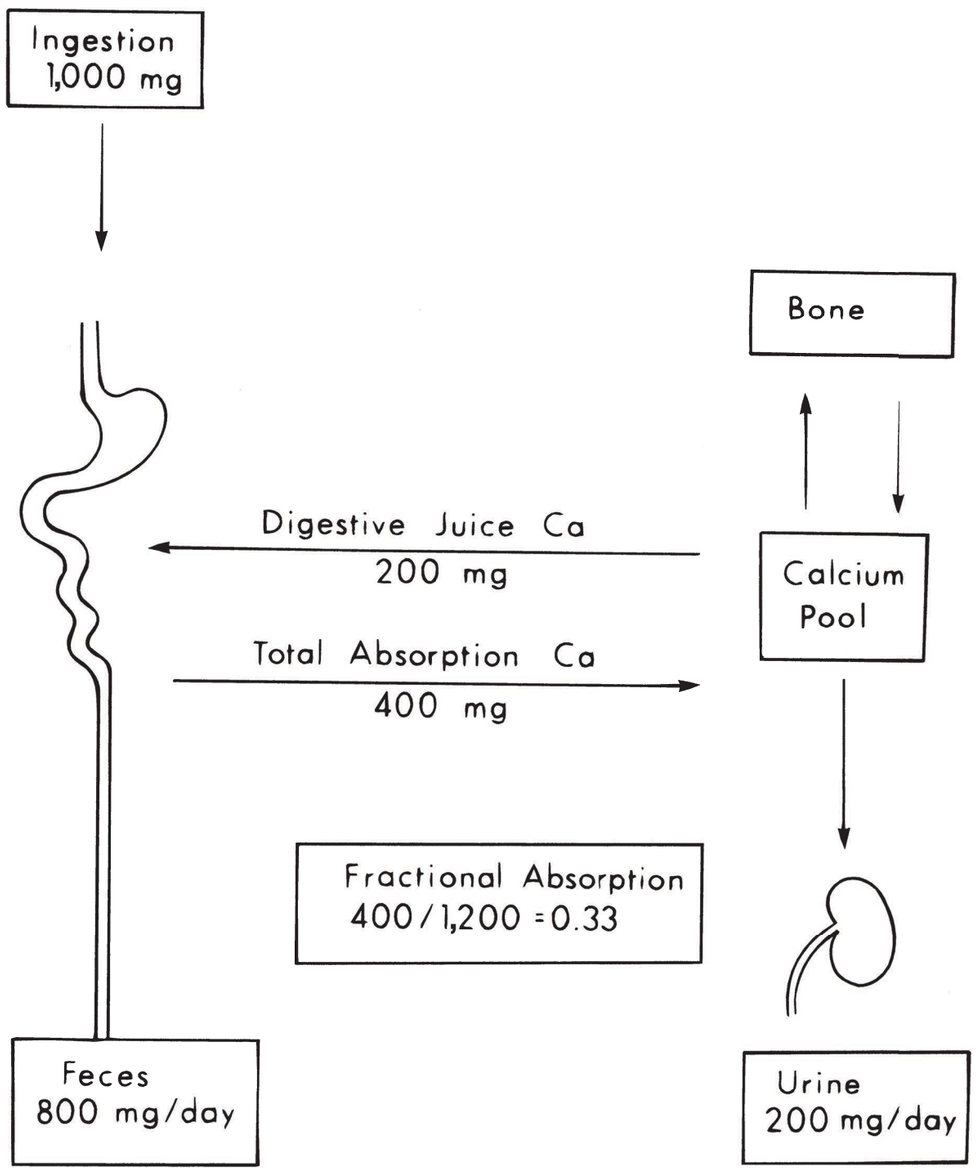


FIGURE 73.10 Diagrammatic representation of Ca metabolism in humans showing the contribution of the gastrointestinal tract, the kidney, and bone to the maintenance of the Ca pool.

the intestine daily. The secreted digestive juice Ca is known as endogenous fecal calcium. The amount of Ca secreted by the intestine is fairly constant and is not greatly influenced by hypercalcemia.

Intestinal Calcium Absorption

The mechanisms of Ca transport across the intestinal mucosa are complex, but our understanding of the physiology is rapidly improving. Intestinal Ca absorption occurs by two general mechanisms: active and passive transport (Fig. 73.11).[690,691] The passive process involves paracellular movement of Ca in some intestinal segments, and active transport involves movement through mucosal epithelial cells. When the intestine is perfused in vitro with increasing Ca concentrations, the rate of movement of Ca from the mucosa to the serosa increases without evidence of saturation or a maximum transport rate. An active transport process would be expected to be saturable. It has been estimated that at luminal Ca concentrations of more than 7.0 mmol per L, Ca is transported primarily by a diffusional process.[95]. This suggests that in regions of the intestine such as the ileum, where the Ca concentration is high, the passive transport process predominates. In the duodenum and jejunum, where the luminal Ca concentration is lower than 6.0 mmol per L, the active transport process assumes a predominant role.[442]

Active intestinal calcium transport involves three steps: (1) the transport of Ca from the lumen into the cell; (2) the movement of Ca within the cell; and (3) the movement of Ca from the cell into the interstitial fluid (Fig. 73.11). Insulation of the cell interior from the millimolar Ca concentrations of plasma suggests that a brush-border component is instrumental in the transfer of Ca into the epithelial cell. The transfer of Ca across the intestinal brush-border surface is modulated by vitamin D.[19,190,383] The early effects of 1,25-dihydroxycholecalciferol on Ca transport are mediated by changes in the structure of the luminal membrane of the intestine.[543] Administration of 1,25-dihydroxycholecalciferol leads to an increase in de novo synthesis and total content of phosphatidylcholine of the BBM. These changes in lipid structure precede or occur simultaneously with the change in calcium transport rate.[543] However, the major mechanism of Ca entry across the intestinal enterocyte brush border of the duodenum, proximal jejunum, and cecum is through a channel, TRPV6,[267,270] which shares high

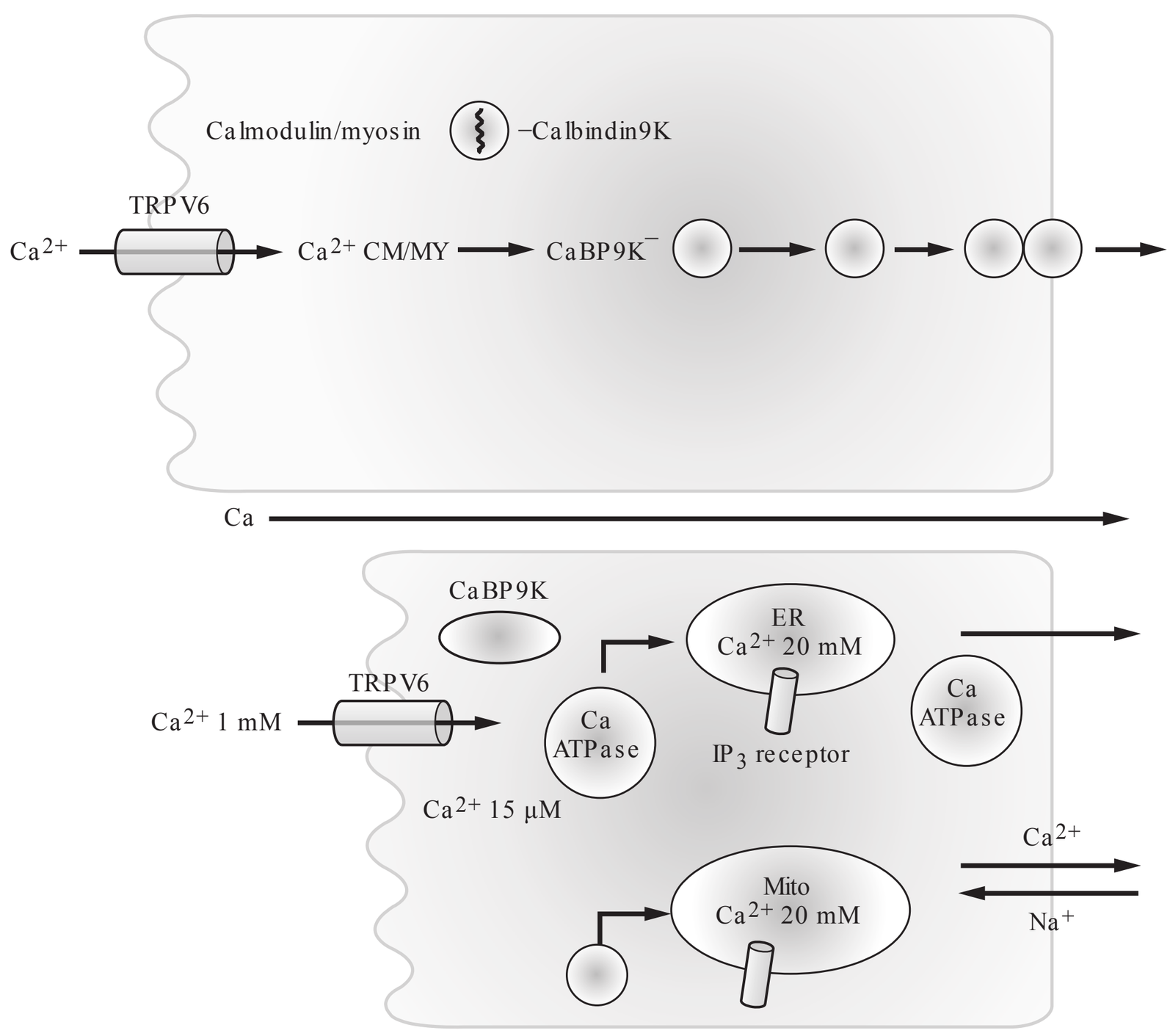


FIGURE 73.11 Intestinal Ca transport in jejunal enterocytes. Ca transport may be through the paracellular space or by an active process through the cell. Transport of Ca from the jejunal lumen through the microvillar membrane is through the TRPV6 channel. Ca is shuttled down the microvillar stalk by calmodulin/myosin (CM/MY) to the glycocalyx where it is bound to calbindin 9Kand vesicle sequestered, Ca vesicles deliver Ca to the endoplasmic reticulum and to the efflux pathway, a Ca ATPase in the basolateral membrane.

homology (75%) with the renal tubular epithelial calcium channel (TRPV5).[283,482] The TRPV acronym stands for the Transient Release Potential (TRP), family of Ca channels of the Vanilloid (V) receptor type, TRPV.[283] TRPV6 is voltage-dependent and permeant to Sr and Ba but not Mg. It is inhibited by the trivalent cations Gd and La, and the divalent Cd and Co.[267,270,271]

Less is known about the movement of Ca within the intestinal cell. When Ca enters the cell, it either diffuses or is carried across the cell to the basolateral membrane, where it is pumped out into the serosal medium. Studies suggest that Ca entering through the apical membrane is accumulated in subcellular organelles within the terminal web of the microvillus. This process is stimulated by 1,25-dihydroxycholecalciferol through nongenomic mechanisms.[322] Calmodulin is the major Ca binding protein in the microvillus.[62,63] Its concentration in the microvillus is increased by 1,25-dihydroxycholecalciferol by redistribution from the cytosol. No new calmodulin synthesis is required or observed after 1,25-dihydroxycholecalciferol administration.[62] Calmodulin is thought to play a major role in Ca transport within the microvillus, whereas calbindin is thought to be the dominant Ca binding protein in the cytoplasm. The hypothesis put forth by Bikle et al.[62,63] is that calmodulin and myosin 1 regulate Ca movement within the microvillus to where Ca accumulates within intracellular organelles through the action of calbindin. Movement in the intracellular organelle provides Ca access to the efflux mechanisms. Thus, Ca is transported across the cell without affecting cytoplasmic Ca levels. Specific Ca binding proteins have been demonstrated in the mucosal cells of the intestine of many species.[657,692–694] Their molecular weights are 8,000 to 25,000 and they are referred to as calbindins. Calbindins are transcriptionally regulated by vitamin D, and calbindin-$_{9K}$ is present in intestinal mucosal cells, whereas calbindin-$_{25K}$ is present in distal renal tubular cells involved in active transepithelial Ca^{2+} transport and the brain, but not in bone or other cells. The time course of the calbindins' appearance after vitamin D treatment is similar to the time course of changes in Ca transport, and they are localized in the glycocalyx surface of the brush border of the mucosal intestinal cells. The exact role of these proteins in Ca transport by mucosal cells is still unknown, but it appears to be related to movement of Ca from the entry channel to a shuttle mechanism delivering it to the cell exit mechanism (Fig. 73.11). Increased intestinal Ca absorption is accompanied by an increase in calbindin levels without changes in their intrinsic binding affinity (K_m) for Ca.

Calcium movement from the mucosa to the serosal surface of the intestinal epithelia occurs against a concentration gradient. The intestinal cells contain a "pump" capable of moving calcium against an electrochemical gradient,[109] a Ca-dependent ATPase that is increased by vitamin D.[639] The increase in Ca ATPase parallels the change in Ca transport after vitamin D repletion. Delivery of intracellular Ca to the exit pump is a process largely unknown but appears to involve calbindins.

Many factors regulate intestinal Ca absorption including (1) dietary Ca intake; (2) vitamin D intake; (3) age of the patient; (4) the general state of Ca balance; and (5) circulating levels of PTH, which all affect active transport. In addition to PTH and vitamin D, other factors such as phosphate influence Ca absorption. High-phosphate diets decrease Ca absorption, possibly due to the formation of relatively insoluble calcium–phosphate complexes that decrease the availability of Ca for transepithelial uptake and to decreased 1,25-dihydroxycholecalciferol synthesis secondary to hyperphosphatemia. Experimentally, large concentrations of lactose or other sugars (mannose, xylose) or certain amino acids (lysine, arginine) inhibit intestinal Ca absorption. The physiologic significance of these observations is unknown. The decreased Ca absorption produced by glucocorticoids has therapeutic implications in the management of hypercalcemic disorders associated with excessive intake or increased sensitivity to vitamin D.

Renal Handling of Calcium

In humans who have a GFR of 170 L per 24 hours and serum ultrafiltrable Ca concentrations of 6 mg per dL, roughly 10 g of Ca is filtered per day. The amount of Ca excreted in the urine usually ranges from 100 to 200 mg per 24 hours; hence, 98% to 99% of the filtered load of Ca is reabsorbed by the renal tubular epithelium (Fig. 73.12). There are remarkable similarities in the handling of Ca and Na by the kidney. Less than 2% of their filtered load is excreted normally, and there is no evidence of tubular secretion of either Ca or Na in the mammalian nephron. Urinary excretion of either Na or Ca is controlled by adjustments in tubular reabsorption. Approximately 60% of the filtered Ca is reabsorbed in the PCT (Fig. 73.12), 20% to 30% in the loop of Henle, 10% by the distal convoluted tubule, and 1% by the collecting system. The terminal nephron (connecting segment, distal tubule, and collecting duct), although responsible for the reabsorption of only 10% of the filtered Ca load, is the major site for regulation of Ca excretion.

Calcium in the Glomerular Filtrate

Micropuncture studies of the kidney in the Munich-Wistar rat with surface glomeruli have demonstrated that the ratio of Ca in fluid of Bowman's space to plasma (TF/P calcium) is 0.6, indicating that only the serum Ca not bound to protein is filterable.[256] Thus, approximately 60% of the total Ca, which is the ultrafiltrable Ca, is filtered across the glomerulus.

Proximal Convoluted Tubule

Potential factors regulating Ca reabsorption in the PCT include convection (solvent drag), concentration (increased Ca concentration in tubular fluid due to absorption of Na and water), and transepithelial potential difference. Microperfusion studies of the rabbit PCT in vitro[73,474] and micropuncture of the rat in vivo[672] indicate that fluid absorption and

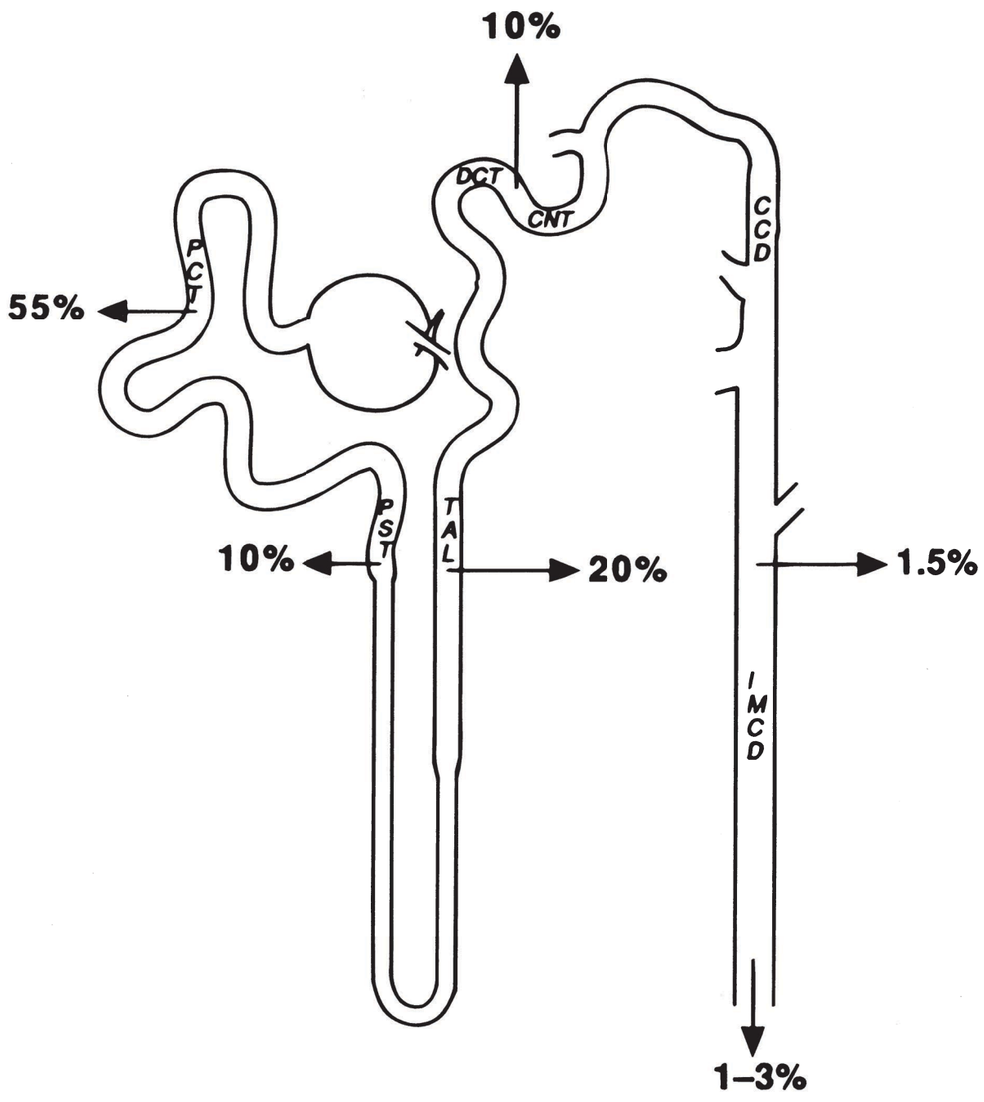


FIGURE 73.12 Schematic illustration of the reabsorption of calcium by different segments of the nephron. *CCD*, cortical collecting duct; *CNT*, connecting tubule; *DCT*, distal convoluted tubule; *IMCD*, intramedullary collecting duct; *PCT*, proximal convoluted tubule; *PST*, proximal straight tubule; *TAL*, thick ascending limb. (From Friedman P, Gesek F. Calcium transport in renal epithelial cells. *Am J Physiol.* 1993;264:F181, with permission.)

solvent drag, as well as diffusion along an electrochemical gradient, contribute to net Ca flux. The reabsorption of Ca in the PCT parallels that of Na and water: The ratio of tubular fluid to plasma ultrafiltrable calcium in the earliest portion of the PCT rises to 1.1 and remains at this value along the rest of the PCT. This is compatible with passive Ca reabsorption secondary to Na and water reabsorption along most of the PCT. The transepithelial movement occurs through the paracellular pathway across the tight junction. Although the passive movement of Ca through a paracellular pathway accounts for most of the Ca transport across the proximal tubule, there is evidence of an active transport component in this segment of the nephron (Fig. 73.13).[73,171,201,356,672] During stop-flow microperfusion experiments measuring net PCT efflux, Ullrich et al. demonstrated that the tubular fluid Ca concentration was lower than that in the capillary.[672] They calculated the active transport rate as 3.4×10^{-13} mol/cm/second, which is in the range of 20% to 30% of the total reabsorptive rate for this segment.

The reabsorption of Ca transcellularly rather than through intercellular channels is a multistep process in which Ca enters the cell across apical membranes and exits across basolateral plasma membranes. Calcium-permeable channels in PCT cells have been described.[189,438–440] However, these are activated by membrane stretch and, therefore, are thought to participate in cell volume regulation.[439] Basolateral efflux of calcium PCTs may be mediated in whole or in part by Na^+-Ca^{2+} exchange.[167,199,583,672,727]

Proximal Straight Tubule (Pars Recta)

Calcium is transported in the pars recta by a process that is not inhibited by ouabain.[560] Because ouabain abolishes water and sodium transport, this suggests that the sodium–calcium exchange is not the major mechanism for Ca extrusion across the basolateral membrane in this segment of the nephron. Approximately one third of the Ca transported can be attributed to sodium and water, and thus, it would seem that an active transport component plays an important role in the reabsorption of Ca in the proximal straight tubule.

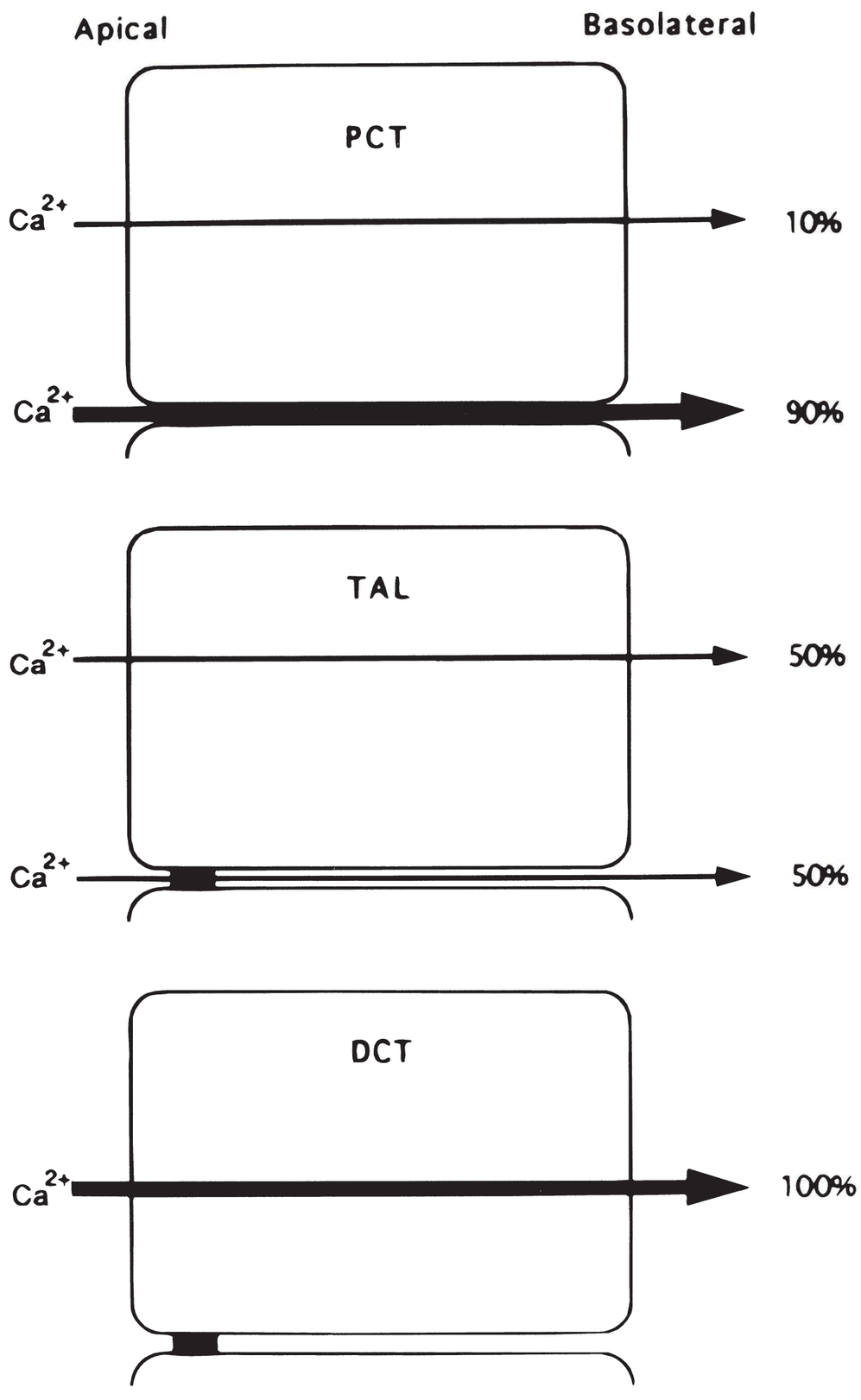


FIGURE 73.13 Cellular and paracellular calcium transport pathways along the nephron. Relative percentage of calcium absorbed by cellular or paracellular pathways in the proximal convoluted tubule (*PCT*), thick ascending limb (*TAL*), and distal convoluted tubule (*DCT*). (From Friedman P, Gesek F. Calcium transport in renal epithelial cells. *Am J Physiol.* 1993;264:F181, with permission.)

Loop of Henle

Neither the thin descending limb nor the thin ascending limb (TAL) of the loop of Henle plays an important role in calcium reabsorption.[560] In contrast, in vitro studies have shown that the TAL of the loop of Henle reabsorbs Ca from lumen to both in the absence of water movement. About 20% of the filtered Ca is reabsorbed in this segment of the nephron. The transepithelial flux of Ca is proportional to the positive transepithelial potential gradient generated by sodium chloride transport mechanisms.[81,591,593] Much of this flux is probably paracellular (Fig. 73.13). Studies of the TAL suggest that the flux ratio for Ca may be greater than can be accounted for by the positive intraluminal potential; thus, an additional active transport process for Ca is present in this segment,[292,552,651] and it accounts for up to 50% of the total Ca transported (Fig. 73.13). This transcellular component is regulated by PTH[201,552] and calcitonin in the cortical and medullary TALs, respectively.[201,651]

Under resting conditions, Ca^{2+} transport is passive in the TAL. Changes in the electrochemical drive for Ca^{2+} determine the magnitude of passive, paracellular absorption. Under these circumstances, the transepithelial voltage is the primary determinant of the driving force, and the magnitude of the voltage, oriented electropositive in the lumen, is set by the rate of Na^+ absorption. As Na^+ absorption increases, transepithelial voltage increases[198,261] and Ca^{2+} flux increases. Peptide hormones that enhance Na^+ transport and thereby increase the transepithelial voltage in medullary TALs would be expected to stimulate passive Ca^{2+} absorption. Extensive evidence consistent with this model has been provided.[158,162,180] Inhibition of Na^+ absorption reduces the transepithelial voltage and would be expected to decrease passive Ca absorption. Furosemide, bumetanide, and ethacrynic acid, which block sodium transport in the TAL of the loop of Henle, also block Ca transport. The tight junction of the TAL has a specific permeability for Ca that participates in the voltage-dependent paracellular flux of the cation. This was proven by the discovery that mutations in the gene PCLN1 which encodes for the protein Paracellin-1 (PCLN1), a member of the claudin family of epithelial tight junction proteins,[207] cause a syndrome of renal magnesium wasting, hypercalciuria, and nephrocalcinosis.[613]

Distal Convoluted Tubule, Connecting Tubule, and Collecting Tubule

Calcium transport in the distal convoluted tubule, connecting tubule, and collecting ducts is an active process. It occurs against an electrochemical gradient. The epithelium is considered "tight," meaning there is very little fluid or electrolyte flux through the paracellular route (Fig. 13).[395] Free flow micropuncture studies in the rat demonstrate that TF_{Ca2+}/UF_{Ca2+} falls from a value of 0.6 in the early PCT to 0.3 by the early portion of the cortical collecting duct. This is consistent with active transcellular calcium movement.

Active transcellular Ca^{2+} absorption in the distal convoluted tubule and connecting tubule is a three-step process. Ca^{2+} enters the cell across apical plasma membranes, diffuses across the cytosol bound to calcium binding proteins, and is actively extruded from the cell across basolateral membranes (Fig. 73.14). The mechanism of Ca^{2+} entry into the cells was defined with the expression cloning of the ECaC (now TRPV5) (Fig. 73.14).[270] Apical influx is considered the rate-limiting step in transcellular Ca transport and, therefore, the regulatory target of stimulatory and inhibitory hormones (Fig. 73.15).[201,634] Evidence suggests that hormonal stimuli of Ca^{2+} transport produce an insertion of Ca channels into the apical membrane (Fig. 73.15).[34,482,634] Furthermore, thiazide diuretics stimulate Ca^{2+} transport in this segment.[605,664] Thiazides produce their diuretic action by inhibiting a Na^+-Cl^- cotransport protein of the apical membrane.[138,605,664] How this is translated into a stimulation of Ca^{2+} transport was elucidated by Shimizu et al.[605] and Bordeau and Lau[83] (Fig. 73.16). In the presence of inhibited apical Na^+ entry, there is increased Na^+ flux into the cell across the basolateral membranes, which is coupled to Ca^{2+} extrusion, in other words actuation of a basolateral Na^+-Ca^{2+} exchanger. This nephron segment is also characterized by a hormonally regulated isoform of the Ca-ATPase, PMCA1b, found only in epithelia involved in active Ca^{2+} transport (Fig. 73.14).[79] In addition, the vitamin D–regulated calcium binding protein, calbindin-$_{28K}$, associated with Ca^{2+} transport is also localized in the distal tubule (Fig. 73.14).[78,395]

The apical Na-Cl cotransport, which is thiazide sensitive, appears mainly in the distal tubule (Figs. 73.16 and 73.17). In the connecting tubule and the collecting duct, Na^+ entry occurs through an apical, amiloride-sensitive Na^+ channel.[395,494,664] Amiloride also stimulates Ca^{2+} reabsorption in these segments. The mechanism appears to be, as for thiazides, a limitation of apical Na^+ entry stimulating basolateral Na^+ entry through a Na^+-Ca^{2+} exchange, activating Ca^{2+} efflux (Figs. 73.16 and 73.17).

Factors that Regulate Calcium Transport

Maneuvers such as administration of parathyroid hormone (PTH),[30,115,197,459,460] cAMP,[593] and calcitonin,[116,524] ECF volume expansion,[10,525] insulin administration,[153,154,526,527] and phosphate depletion[204,357,717] have all been shown to inhibit proximal tubular reabsorption of Ca and increase the delivery of Ca to the more distal nephron segments. The relationship of these maneuvers on urinary Ca excretion, however, may be a decrease, no change, or an increase in Ca excretion, emphasizing again the critical role of the distal tubule in the final regulation of Ca excretion. Both metabolic acidosis[652] and phosphate depletion[41,357,717] are accompanied by increased Ca excretion in the urine. Experimental studies in animals suggest that the "defect" in Ca reabsorption in metabolic acidosis[652] and phosphate depletion[717] is located in the distal tubule and probably through an effect on the TRPV5,[271] although phosphate depletion may also affect Ca transport in the proximal tubule. The administration of sodium bicarbonate, which rapidly corrects acidosis, increases Ca reabsorption in the late distal tubule. Similar

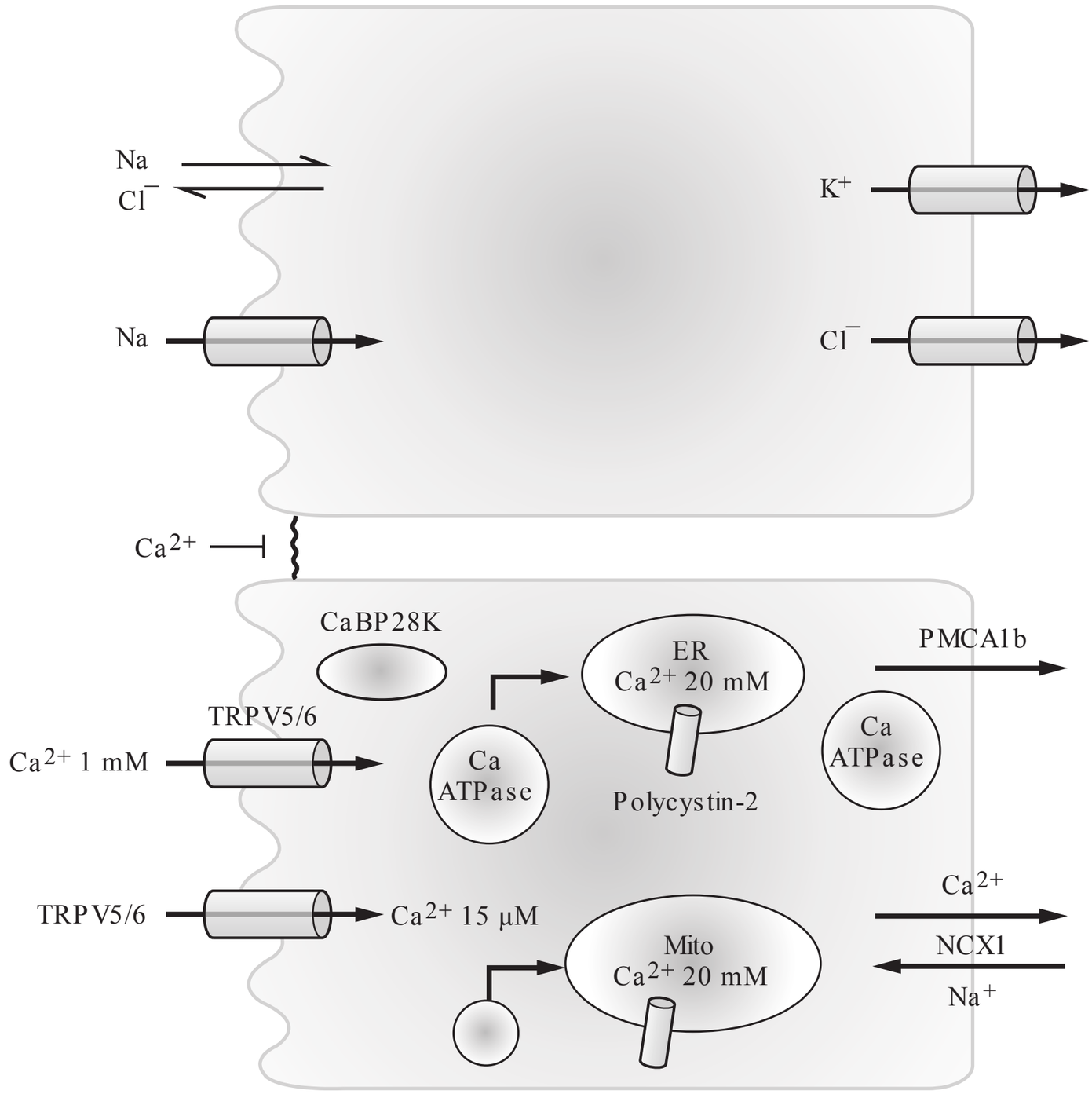


FIGURE 73.14 Calcium transport in distal convoluted tubule and connecting tubule. Transport mechanisms involved in transcellular Ca flux are depicted in the lower cell, whereas other transport proteins whose actions impinge on Ca absorption (apical NaCl cotransport, Na channels, basolateral chloride channels, and basolateral potassium channels) are shown in the top cell. There is no paracellular flux. The apical NaCl cotransport is inhibited by thiazide diuretics whose action in Ca transport is thought to be a limitation of Na availability leading to increased activity in the basolateral Na/Ca exchange, NCX1, causing increased Ca efflux. Likewise, the epithelial Na channel is inhibited by amiloride diuretics whose action also stimulates Ca transport similar to thiazide diuretics. Ca entry is facilitated by the apical epithelial Ca channel TRPV6/5 which assembles as homo- or heterotetramers. Subsequently, the ion binds to CABP28K and may be delivered to the endoplasmic reticulum. The ER may come into close association with PMCA1b resulting in delivery of Ca to the efflux pathways.

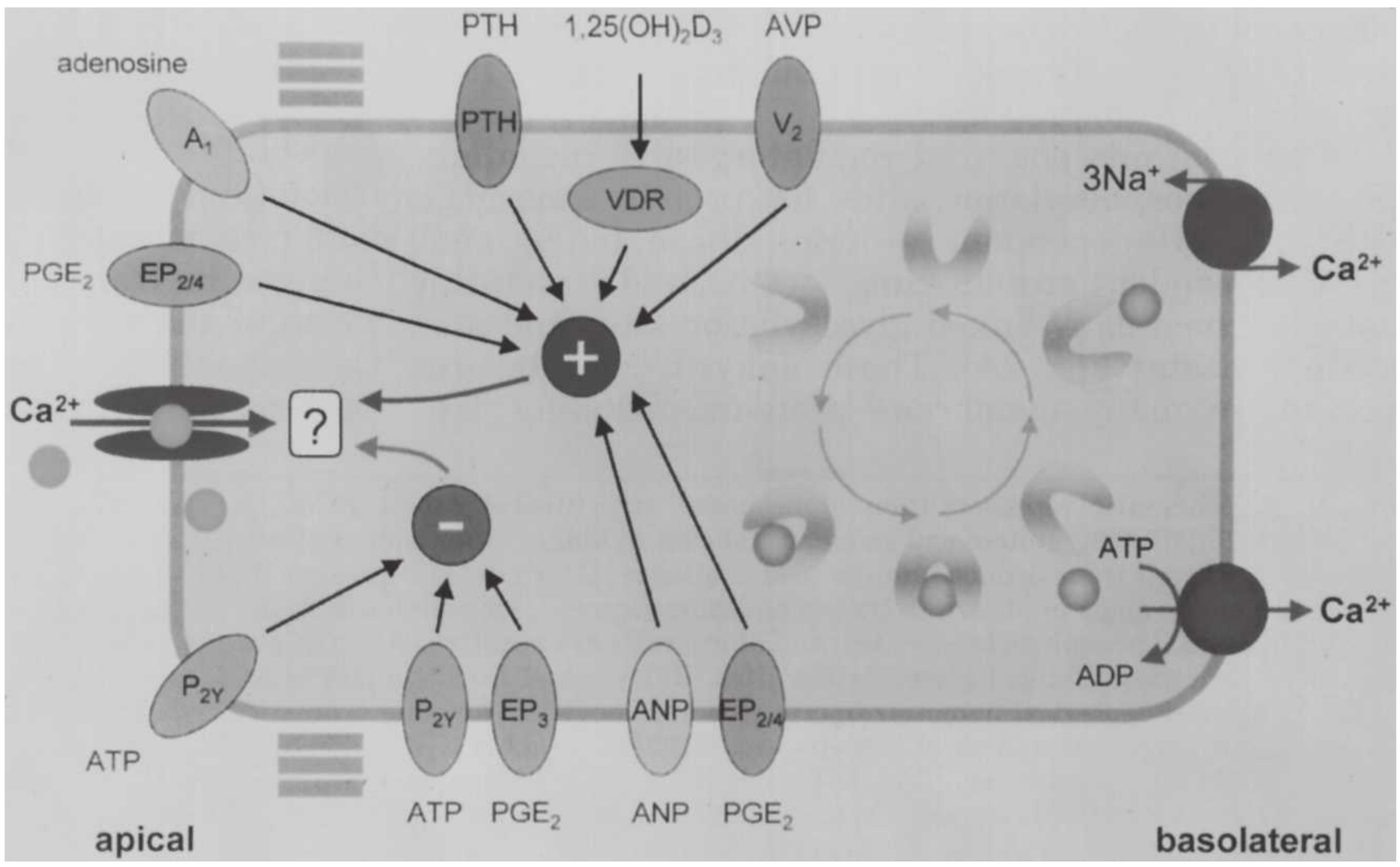


FIGURE 73.15 Schematic model for hormonal regulation of transcellular Ca^{2+} transport in distal nephron. Parathyroid hormone (PTH), V_2, atrial natriuretic peptide (ANP), and EP_3 receptors are localized in the basolateral membrane, whereas A_1 is present in the apical membrane. $EP_{2/4}$ and P_{2Y} are present in both membranes. 1,25-dihydroxycholecalciferol passes plasma membranes and binds to the intracellular vitamin D receptor (VDR). Hormones can be divided into stimulatory hormones, including PTH, arginine vasopressin, ANP, prostaglandin E_2 (PGE_2) (via $EP_{2/4}$), and adenosine, and inhibitory hormones such as adenosine triphosphate and PGE_2 (via EP_3). (From Hoenderop JG, Willems PH, Bindels RJ. Toward a comprehensive molecular model of active calcium reabsorption. *Am J Physiol Renal.* 2000;278:F352, with permission.)

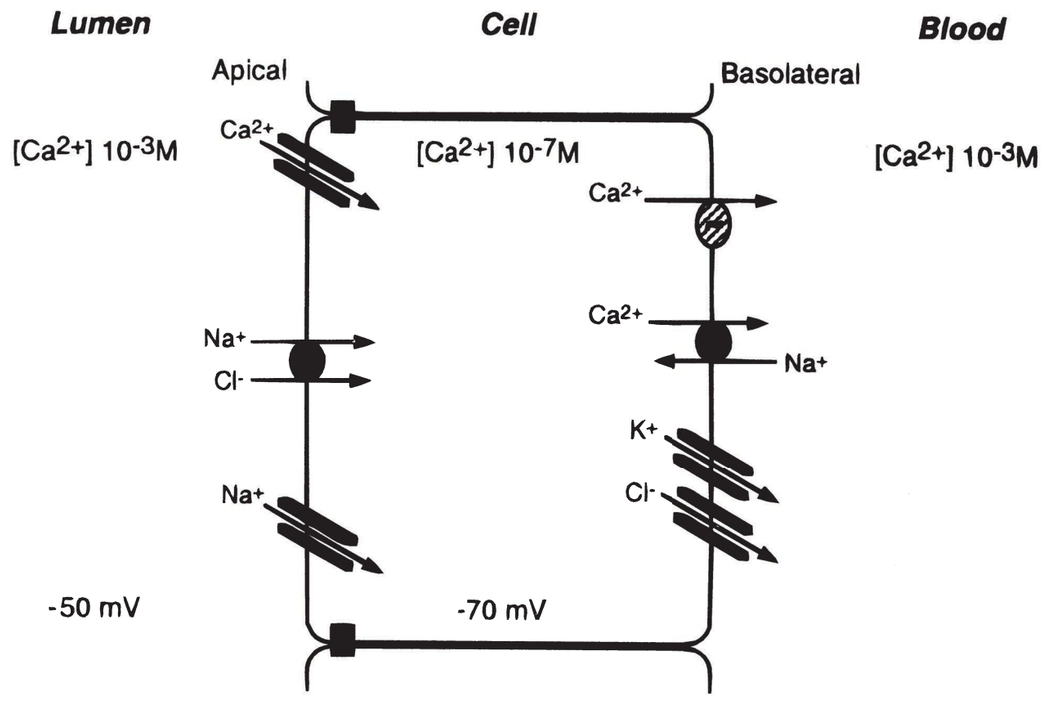


FIGURE 73.16 Model of Ca^{2+} transport in distal convoluted tubule, connecting tubule, and cortical collecting duct cells. Transport mechanisms involved in apical Ca^{2+} entry (channels) and basolateral efflux (Ca^{2+}-ATPase and Na^{+}-Ca^{2+} exchange) are depicted. Other transport proteins whose action impinges on Ca^{2+} absorption (apical Na^{+}-Cl cotransport, Na^{+} channels, basolateral Cl channels, and basolateral K^{+} channels) are shown. The apical Na^{+}-Cl cotransport is inhibited by thiazide diuretics whose action on Ca^{2+} transport is thought to be a limitation of Na^{+} availability leading to increased activity of the basolateral Na^{+}-Ca^{2+} exchange causing increased Ca^{2+} efflux. This would assume basal activity of Ca^{2+} channel activity. The dependency of the thiazide effect on the presence of parathyroid hormone (PTH) would be expected because PTH stimulates insertion of Ca^{2+} channels into the apical membrane. (From Friedman P, Gesek F. Calcium transport in renal epithelial cells. *Am J Physiol.* 1993;264:F181.)

results are found when phosphate is given to an animal that has been previously phosphate depleted.

PTH plays an important role in the regulation of Ca transport and reduces urinary Ca excretion (Fig. 73.15). In humans, the status of the parathyroid gland greatly influences the amount of Ca excreted in the urine. At equal filtered loads of Ca, patients with high levels of circulating PTH have less Ca in the urine than those in whom the levels of PTH in serum are low. Experimental evidence indicates the main effect of PTH is in the distal tubule and connecting tubule[30,197,605–607] and is mediated through the adenylate cyclase system. Although PTH inhibits proximal tubular reabsorption of Na and Ca, the main action of PTH is localized in more distal segments of the nephron.

Studies in rabbits have shown a PTH-sensitive Ca transport mechanism in the cortical TAL.[459,460] Little is known about how PTH affects the paracellular pathway for Na^{+} and Ca^{2+} reabsorption of the PCT. Studies in isolated renal cortical BBM vesicles indicate that PTH mimics the effect of membrane phosphorylation on Ca binding and translocation.[320,634] Phosphorylation of BBM vesicles produces an increase in membrane-bound Ca due to production of negatively charged phospholipids.[282] Aminoglycosides compete for the binding of Ca to phospholipids. In the presence of a chemical potential for Ca, PTH also stimulates Ca binding that is aminoglycoside inhibitable, as well as an increase in the BBM content of the acidic phospholipids produced by phosphorylation.[282] The control of Ca efflux across the basolateral membrane of the PCT by PTH involves the Na^{+}-Ca^{2+}

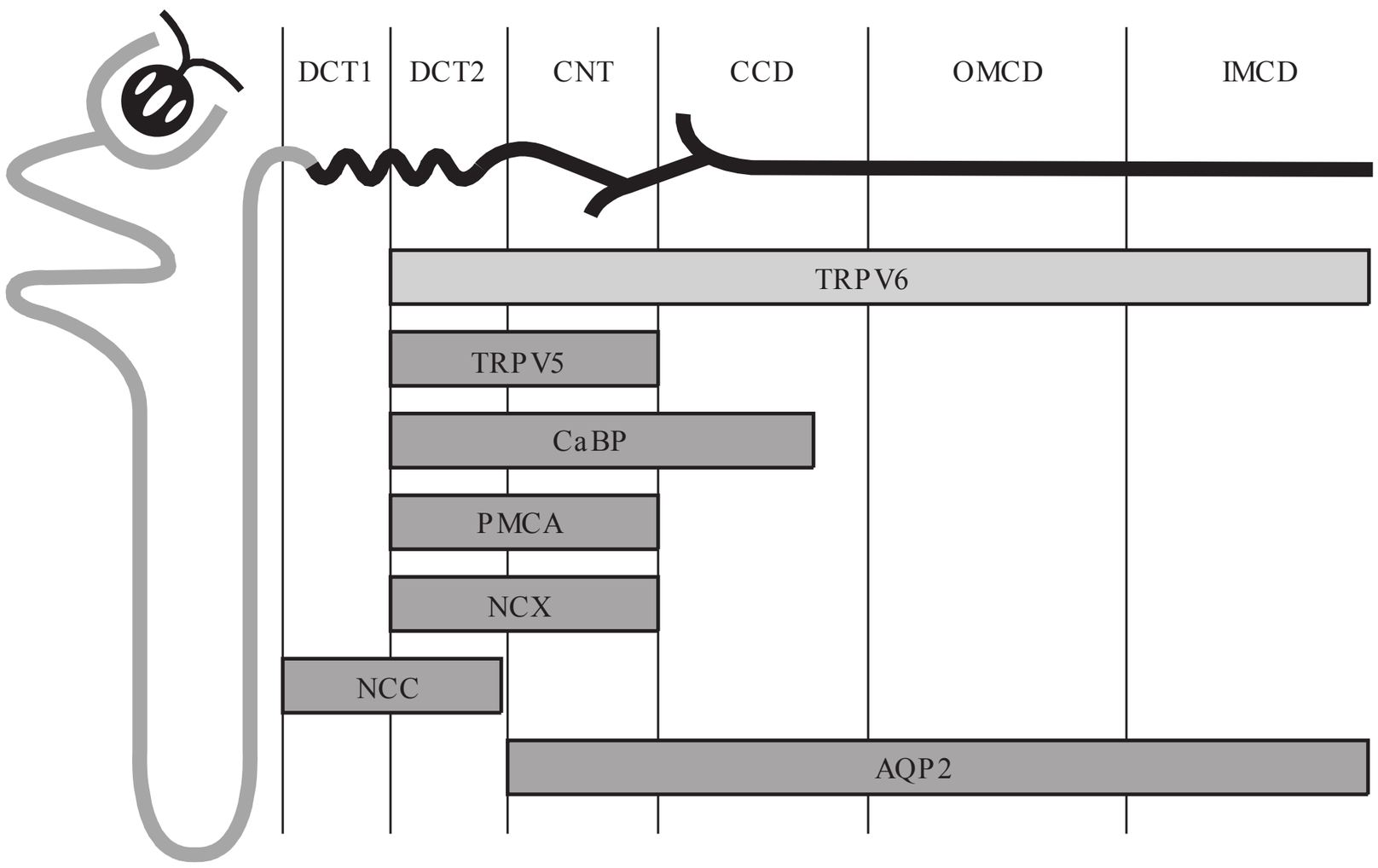


FIGURE 73.17 Renal distribution of TRPV6 in mouse kidney. Summary of the renal distribution of TRPV6 as determined by immunohistochemistry. *DCT*, distal convoluted tubule; *CNT*, connecting tubule; *CCD*, cortical collecting duct; *OMCD*, outer medullary collecting duct; *IMCD*, inner medullary collecting duct; *PMCA*, plasma membrane Ca^{2+}-ATPase; *NCX*, Na^{+}/Ca^{2+} exchanger; *NCC*, Na^{+}-Cl^{-} cotransporter; *AQP2*, aquaporin-2. (From Nijenhuis T, Hoenderop JG, vander Kamp AW, et al. Localization and regulation of the epithelial Ca^{2+} channel TRPV6 in the kidney. *J Am Soc Nephrol.* 2003;14:2731, with permission.)

exchange. Scoble et al.[583] and Jayakumar et al.[302] demonstrated sodium gradient (outside > inside) dependent on Ca efflux stimulated by PTH in basolateral membrane vesicles from dog and rat renal cortex. These studies were thought to use membranes from the proximal tubule. However, more recent studies suggested that the Na^+-Ca^{2+} exchange activity is the highest in the distal tubule and the earlier studies may have been affected by contaminants from these segments.[541]

PTH stimulation of Ca^{2+} transport in the TAL of the loop of Henle is localized to the cortical portion, whereas the calcitonin effect is exerted in the medullary portion. Because PTH does not stimulate Na^+ or Cl^- transport, it is unlikely that it works to increase the lumen-positive transepithelial electrical driving force. Rather, its main action has been suggested to be at the level of the permeability to Ca^{2+} of the paracellular pathway[80,82] and to be related to the function of paracellin-1 (PCLN1), also referred to as claudin-16, the tight junction Ca/Mg permeability factor. Recent thought indicates that an effect on transcellular transport may be involved.[197,200]

Significant progress has been made in the understanding of PTH actions on Ca^{2+} transport in the connecting tubule and the cortical collecting duct. Here, Ca^{2+} reabsorption is transcellular and an active energy consuming process. Studies[30,197,200,214] suggest that PTH hyperpolarizes the epithelium and produces insertion of voltage-operated Ca^{2+} channels in the apical membrane.[34,200] Patch clamp studies of PTH-stimulated distal convoluted tubule cells[200,215,538,540] demonstrated an increase in open time of apical membrane channels with increasing membrane voltage.[652] However, these findings remain controversial,[200,214,215] and the mechanism of anomalous function of the apical Ca entry channel remains to be elucidated. Voltage-operated epithelial Ca channels are complex heterotetramers consisting of TRPV5 and TRPV6 subunits (Fig. 73.16).[269] Identification of the distal nephron Ca entry channel, TRPV5 (Fig. 73.14),[268,270,271] which is insensitive to membrane potential, failed to shed light on the mechanism of Ca entry associated with hyperpolarization,[728] and although the discovery of heterotetramers may explain the divergent electrophysiologic results,[269] other Ca entry mechanisms probably await discovery.

Hypocalcemia

Hypocalcemia decreases the renal excretion of Ca, secondary to a decrease in the filtered load of Ca and enhanced tubular reabsorption of Ca. Hypocalcemia triggers the release of PTH, which increases Ca reabsorption in the TAL and distal tubule. The effects on the TAL could also be observed in the TPTX setting.[529] Recent studies have indicated that the Ca sensor receptor (CaSR) inactivation plays an important role in the enhancement of Ca transport in the TAL during hypocalcemia.[30,97,260]

Hypercalcemia

In general, patients with hypercalcemia have increased amounts of v in the urine, partly due to an increase in the filtered load of Ca and partly to suppression of PTH secretion. Activation of the CaSR also may increase the excretion of Ca by decreasing the activity of the apical K^+ channel and decreasing the positive potential difference (PD). Thus, less Ca and Mg are reabsorbed via the paracellular pathway in the TAL.[30,97]

Volume Status

Volume contraction decreases and volume expansion increases the renal excretion of Na and Ca. Volume expansion decreases tubular reabsorption of both Na and Ca even if the filtered load is reduced,[431] clearly demonstrating that the regulation of these ions is primarily by changes in tubular reabsorption.

Diuretics

Furosemide produces a significant increase in Na^+ and Ca^{2+} excretion by inhibiting the reabsorption of both ions in the TAL.[179] Furosemide decreases the PD in the TAL. Because the reabsorption of Ca in this segment of the nephron is passive, a decrease in the positive voltage of the lumen diminishes the movement of Ca through the paracellular pathway. Thiazide, on the other hand, produces dissociation between Na and Ca excretion. A mild natriuresis is usually accompanied by a decrease in Ca excretion. Micropuncture studies have shown that this mechanism occurs in the distal portion of the nephron. Thiazide stimulates Ca entry through the apical Ca^{2+} channel by activating Cl channels (Fig. 73.13).[213] These effects are independent of PTH, although PTH is important for the presence of TRPV5 in the apical membrane of the connecting tubule. The chronic administration of thiazide produces significant decrease in Ca excretion secondary to volume contraction, because this effect can be reversed by the administration of NaCl.

Vitamin D

The acute administration of 1,25-dihydroxycholecalciferol increases renal transepithelial Ca transport by its effects on the distal, connecting, and collecting duct system. In these segments of the nephron, the transport of Ca is mainly active. 1,25-Dihydroxycholecalciferol has a positive transcriptional effect on TRPV5 gene transcription. In addition, an increase in calbindin-28K and on the Ca ATPase in the basolateral side of the cell is also transcriptionally regulated by 1,25-dihydroxycholecalciferol (Fig. 73.15).[271]

The chronic administration of 1,25-dihydroxycholecalciferol increases the excretion of Ca secondary to an increase in the filtered load of Ca. This is due to an increase in Ca absorption in the gut and Ca resorption in the skeleton.

Clinical Effects of Plasma Calcium Concentrations

Hypocalcemia

The clinical manifestations of hypocalcemia vary greatly among patients.[581] Patients who suddenly become hypocalcemic, such as those with postsurgical hypoparathyroidism,

may develop profound symptomatology, including tetany, even after a moderate decrease in serum Ca levels. On the other hand, patients with chronic renal insufficiency adjust well to low levels of serum Ca and seldom become symptomatic. Before the pathophysiologic mechanisms responsible for the hypocalcemia can be correlated with the clinical symptomatology, it is critical to determine whether both total and ionized Ca levels are low. In conditions such as the nephrotic syndrome and cirrhosis with severe hypoalbuminemia, total serum Ca may be decreased, but ionized Ca levels may be within the normal range or only slightly decreased, and the patient remains asymptomatic.

Clinical Symptoms

Patients with significant hypocalcemia have increased neuromuscular irritability.[411] The hallmark of hypocalcemia is tetany. Latent tetany may be detected by tapping over the facial nerves, which results in contraction of the facial muscles (Chvostek's sign), or by occluding the arterial blood supply to the forearm, which produces carpal spasm (Trousseau's sign). The symptomatology depends on the rapidity of onset of hypocalcemia. Patients with chronic renal failure occasionally have marked hypocalcemia; however, tetany is extremely rare. This may be due in part to the presence of metabolic acidosis. However, the changes in ionized Ca produced by metabolic acidosis in the majority of patients with profound hypocalcemia are not sufficient to bring the ionized Ca level back to normal. On the other hand, respiratory alkalosis due to hyperventilation can precipitate tetany. Clinically, the patient may complain of tingling in the tips of the fingers, stiff muscles, and cramps and may develop convulsions or impaired mental function. Children may develop mental retardation, and dementia may occur in adults. Extrapyramidal disorders also have been found in some patients. Psychiatric manifestations are characterized by confusion and hallucinations. Proximal muscle weakness is more frequently seen when the hypocalcemia is secondary to vitamin D deficiency.

Severe complications of hypocalcemia include development of cataracts,[293] papilledema, and rarely, optic neuritis. In general, the skin may be dry and puffy, and the patient may develop dermatitis. Hypocalcemia may produce hypotension and a delay in ventricular repolarization, thus increasing the QT interval and ST segment. Ventricular arrhythmias and atrial fibrillation refractory to digoxin[126] have been seen in patients with hypocalcemia. Because Ca, as mentioned previously, has an inotropic effect, hypocalcemia may be responsible in part for a decrease in cardiac output.[100,135,216]

The pathogenetic mechanisms responsible for the development of hypocalcemia are described in Table 73.6 and include: (1) absence of PTH; (2) decreased Ca mobilization from bone; (3) reduced Ca absorption in the gastrointestinal tract; (4) translocation of Ca between different compartments of the body; and (5) miscellaneous conditions.

73.6 Causes of Hypocalcemia

I. Hypocalcemia secondary to low or absent levels of parathyroid hormone in blood
   - A. Hypoparathyroidism
     1. Congenital
     2. Idiopathic
     3. DiGeorge syndrome
     4. Postsurgical
     5. Infiltration of parathyroid glands by malignancy or amyloidosis
   - B. Transient hypoparathyroidism
     1. Neonatal
     2. Postsurgical (for parathyroid adenoma)

II. Hypocalcemia secondary to a decrease in calcium mobilization from bone
   - A. Vitamin D deficiency
     1. Decreased ingestion
     2. Decreased absorption (gastrointestinal disorders)
        - a. Partial gastrectomy
        - b. Intestinal bypass
        - c. Sprue
        - d. Pancreatic insufficiency
   - B. $25(OH)D_3$ deficiency
     1. Severe liver disease
        - a. Biliary cirrhosis
        - b. Amyloidosis
     2. Ingestion of anticonvulsant medication
     3. Nephrotic syndrome
   - C. $1,25(OH)_2D_3$ deficiency
     1. Advanced renal failure
     2. Severe hyperphosphatemia
     3. Hypoparathyroidism
   - D. Pseudohypoparathyroidism types I and II
   - E. Magnesium deficiency

III. Hypocalcemia secondary to reduced calcium absorption in the gastrointestinal tract
   - A. Deficiency of vitamin D or its metabolites

IV. Hypocalcemia secondary to translocation of calcium into different compartments
   - A. Hyperphosphatemia
   - B. Administration of citrate
   - C. Administration of ethylenediaminetetraacetic acid
   - D. Urinary excretion

V. Miscellaneous conditions
   - A. Ca receptor gene mutations
   - B. Pancreatitis
   - C. Colchicine intoxication
   - D. Pharmacologic dose of calcitonin
   - E. Administration of mithramycin
   - F. "Hungry bone" syndrome

From Slatopolsky E. Pathophysiology of calcium, magnesium, and phosphorus. In: Klahr S, ed. The Kidney and Body Fluids in Health and Disease. New York: Plenum Press; 1983:269, with permission.

Hypocalcemia Secondary to Low or Absent Levels of Parathyroid Hormone in Blood

A decrease or absence of PTH will have significant effects on Ca metabolism.[373,475,597] Because PTH plays a key role in the regulation of osteoclasts, which are the cells responsible for bone resorption, through the production of RANKL, a decrease in the activity or in the number of osteoclasts will eventually reduce the efflux of Ca from bone. In the absence of PTH, the capacity of the ascending portion of the loop of Henle and distal nephron to transport Ca is decreased; thus, at any filtered load of Ca, a greater amount of Ca will be excreted in the urine. Moreover, the absence of PTH decreases the activity of 1α-hydroxylase in the kidney and leads to decreased formation of 1,25-dihydroxycholecalciferol and a reduction in Ca absorption from the GI tract. Thus, decreased mobilization of Ca from bone, excretion of larger amounts of Ca in the urine, and decreased absorption of Ca from the gut lead to profound hypocalcemia. The most common cause of hypoparathyroidism is excision or damage to the parathyroid glands at surgery. This may be secondary to thyroid or parathyroid surgery or to radical neck dissection performed for the treatment of cancer.[149,575] Some patients might develop transient hypocalcemia. This phenomenon is observed in patients who have one adenoma of the parathyroid gland. The hypercalcemia produced by the excessive secretion of PTH by the adenoma usually suppresses secretion from the other glands, and the removal of the adenoma may produce a transient period of hypoparathyroidism and hypocalcemia. However, the remaining glands, if they are intact, will respond to the hypocalcemia, and this abnormality will be reversible in a relatively short period of time.

Idiopathic hypoparathyroidism is a rare disease, and tetany may occur soon after birth. Idiopathic hypoparathyroidism may be associated with congenital absence of the thymus (DiGeorge syndrome).[161,323,451] These patients have depressed cell immunity and many other malformations; they frequently have mucosal candidiasis and usually die in early childhood of severe hypocalcemia or severe infections.[323] The parathyroid gland may be transiently suppressed at birth as a result of maternal hypercalcemia; thus, neonatal tetany should be looked for in the presence of hypercalcemia of any cause in the mother. The fetal parathyroid glands are suppressed by maternal hypercalcemia and when the hypocalcemic infant is stressed—for example, with a phosphate load (cow's milk)—tetany may result. Another factor that plays a key role in the secretion of PTH is magnesium.[21,118,365,566,649] As will be discussed in a subsequent section, profound hypomagnesemia may decrease the release of PTH. In this syndrome, administration of magnesium to correct the hypomagnesemia increases the release of PTH within minutes.

Hypocalcemia Secondary to Decreased Calcium Mobilization from Bone

Vitamin D has a synergistic effect with PTH that increases the mobilization of calcium from bone. The mechanism by which vitamin D and its metabolites increase bone resorption is not fully understood. Both hormones are key factors in the differentiation of osteoclasts,[642,695] and both factors regulate the osteoblast through differentiation of osteoblast precursors and direct regulation of bone matrix protein gene transcription.[642,695] Many disorders can alter the metabolism of vitamin D, and different vitamin D metabolites could be responsible for decreased mobilization of Ca from bone. In vitamin D–deficient rickets, a nutritional condition observed in children, the lack of vitamin D is responsible for hypocalcemia, hypophosphatemia, and mild secondary hyperparathyroidism.[112,496] Disorders of the GI tract such as partial gastrectomy, intestinal bypass, tropical and nontropical sprue, and Crohn disease may impair the absorption of vitamin D from the diet. Pathologic processes that involve the liver, such as hepatobiliary cirrhosis, may decrease the production of 25-hydroxycholecalciferol.[77] The lack of this metabolite greatly diminishes the mineralization front, and adults with low levels of 25-hydroxycholecalciferol may develop osteomalacia. Although there may be an increase in the level of PTH, osteoclasts are unable to remove Ca because the osteoid material lacks minerals; therefore, there is decreased mobilization of Ca from bone. Administration of anticonvulsant medication may also result in low serum levels of 25-hydroxycholecalciferol, possibly due to the enhanced microsomal activity in the liver with increased catabolism of 25-hydroxycholecalciferol.[129,249,610]

Chronic Renal Failure/1,25$(OH)_2D_3$ Deficiency

Chronic renal failure is characterized by moderate hypocalcemia. Serum calcium seldom falls to less than 7.0 mg per dL. The pathogenesis of hypocalcemia in chronic renal failure is multifactorial. However, phosphate retention and low levels of 1,25-dihydroxycholecalciferol play a key role in its genesis.[128] In patients with profound hypomagnesemia, the skeleton becomes resistant to the action of PTH, and there is decreased Ca mobilization from bone.[365,566]

Pseudohypoparathyroidism

Another important condition causing hypocalcemia is PHP, which is a genetic disorder characterized by skeletal and somatic defects including short stature, rounded face, brachydactyly, subcutaneous calcification, and subnormal intelligence.[15,152,391,423] The secretion of PTH is increased as assessed by elevated levels of immunoreactive PTH; thus, the hypocalcemia in PHP is felt to represent a bone resistance to the effects of PTH.[355,703] This syndrome is collectively referred to as Albright hereditary osteodystrophy (AHO).[376,424] Many patients also have renal resistance to the action of the hormone because administration of exogenous PTH does not lead to increased urinary excretion of cAMP and phosphate. The syndrome has been subclassified as PHP type Ia (PHP-Ia), in which there is neither a cAMP nor a phosphaturic response to exogenous PTH. Maternally

inherited mutations in one of the 13 GNAS exons encoding $G_{S\alpha}$ cause PHP-Ia.[355,375,505] The mRNA for G_S is also reduced about 50% in these patients.[505] Heterozygous mutations of the $G_{S\alpha}$ gene have been identified in families of subjects with AHO, providing molecular confirmation that transmission of the $G_{S\alpha}$ gene defects accounts for the autosomal-dominant inheritance of AHO.[453,702] When the same $G_{S\alpha}$ mutations are inherited paternally, affected individuals develop AHO in the absence of hormone resistance, and this condition is referred to as pseudopseudohypoparathyroidism (PPH).[355] Thus, the development of hormone resistance in a patient with a $G_{S\alpha}$ mutation is subject to paternal imprinting; that is, it develops only after maternal transmission.[355,573,703] Genomic imprinting is a process by which specific genes undergo allele-specific epigenetic changes that lead to allele-specific differences in gene expression. One or more of the epigenetic changes is established in the male or female germline during gametogenesis. Often, imprinting is associated with allele-specific differences in DNA methylation at CpG dinucleotides during gametogenesis and maintained throughout development. Imprinting may be incomplete, as in tissue specific, as is the case for GNAS. $G_{S\alpha}$ is biallelically expressed in most tissues, but in the renal proximal tubule and some endocrine organs, it is expressed primarily from the maternal allele. As a result of this tissue-specific imprinting, patients who inherit $G_{S\alpha}$ null mutations from their mother develop multihormone resistance of PHP-1a.[573]

Some subjects with PHP type I lack features of AHO. Patients with this subtype, termed PHP type Ib (PHP-Ib), typically show hormone resistance that is limited to PTH target organs and have normal $G_{S\alpha}$ activity.[374] This variant has been genetically linked to the GNAS locus on chromosome 20q13-3, and the pattern of inheritance indicates paternal imprinting (maternal transmission). Furthermore, affected individuals with autosomal dominant PHP-Ib show loss of GNAS exon A/B methylation and a heterozygous ~3 kb microdeletion located within STX1b approximately 220kb centromeric of GNAS exon A/B.[355] Hormone resistance in PHP-Ib is limited to the PTH dependent actions in the renal proximal tubule and a few other tissues in which $G_{S\alpha}$ is paternally imprinted such as the thyroid.[355]

PHP type II, in which there is no phosphaturia despite a normal cAMP excretion rate in response to PTH,[117,169,274,325,483,553] is a heterogeneous disorder. Some of these patients have low levels of 1,25-dihydroxycholecalciferol, perhaps representing renal resistance to PTH-stimulated 1α-hydroxylase activity. Thus, the high levels of PTH and the lack of response to the exogenous administration of PTH differentiate this syndrome from true hypoparathyroidism. The hyperphosphatemia that is present in this syndrome also may be partly responsible for the low levels of 1,25-dihydroxycholecalciferol. Thus, PHP is a heterogeneous disorder; some patients have resistance to PTH at the renal level only, others at the skeletal level, and still others in both organs.

Hypocalcemia Secondary to Reduced Intestinal Calcium Absorption

A healthy individual who ingests a low calcium diet usually does not develop hypocalcemia or develops it to a minimal degree because compensatory secondary hyperparathyroidism will correct mild hypocalcemia. Hypocalcemia is usually associated with pathologic processes of the GI tract that affect the absorption of vitamin D. Under these circumstances, the low absorption of calcium, plus abnormalities in vitamin D metabolism, greatly affects calcium homeostasis, and the patient may develop profound hypocalcemia. Growing animals fed a low calcium diet develop severe hypocalcemia.

Hypocalcemia Secondary to Translocation of Calcium into Different Compartments

Precipitation of ionized Ca is seen in disorders in which there is retention of phosphorus. Patients with advanced renal insufficiency, malignancies,[730] or severe rhabdomyolysis and hyperphosphatemia[335] may precipitate Ca rapidly and may develop symptoms characterized by tremors, muscular irritability, and tetany. In the neonate, administration of cow's milk, which is high in phosphorus content compared with human milk, may produce severe hyperphosphatemia and hypocalcemia. Neonatal parathyroid function is not adequate to cope with this challenge, and the neonate may develop severe symptoms secondary to hypocalcemia. When large amounts of blood containing citrate are given to patients (open heart surgery, exchange transfusions for neonatal hyperbilirubinemia), the ionized calcium is complexed by citrate and hypocalcemia leading to tetany may develop.

Hypocalcemia secondary to increased urinary excretion of Ca is rare and self-limited. The expansion of the ECF compartment produces a remarkable decrease in the reabsorption of Na and Ca, and large amounts of these cations may be excreted in the urine. However, these are transitory mechanisms that are rapidly corrected by the release of PTH. Thus, if the PTH, vitamin D, and skeletal axis are intact, an increase in urinary Ca excretion should not result in significant hypocalcemia. Diuretics such as furosemide or ethacrynic acid, which block the reabsorption of Ca in the thick ascending portion of the loop of Henle, are effective drugs in the treatment of hypercalcemia. However, very seldom do patients ingesting these drugs develop hypocalcemia.

Miscellaneous Conditions

Defects in the human CaSRs have been shown to cause familial hypocalciuria, hypercalcemia, and neonatal severe hyperparathyroidism.[127,507,511] Recently, Pollak et al.[513] demonstrated that a missense mutation (GLU128 Ala) in this gene causes familial hypocalcemia in affected membranes of one family. In this syndrome, an alteration in the CaSR shifts the "set point" for calcium to the left, and the parathyroid glands are hyperresponsive to extracellular Ca.

Approximately 10% to 20% of patients with acute pancreatitis develop some degree of hypocalcemia. The

hypocalcemia is related to deposition of calcium salts in areas of lipolysis and tissue necrosis.[250] Some investigators have postulated that proteolytic digestion of PTH may explain the lack of elevated levels of PTH in the serum of patients with acute pancreatitis.

Some drugs such as calcitonin, mithramycin (used for testicular carcinoma), and colchicine (used in gout) can produce profound hypocalcemia by decreasing bone resorption. A series of disorders are characterized by increased bone formation in which the uptake of Ca by the skeleton is greatly increased. Such patients may develop profound hypocalcemia. A disorder known as "hungry bone syndrome" is seen in patients with chronic renal insufficiency and severe secondary hyperparathyroidism. The removal of the parathyroid glands in these uremic patients produces profound hypocalcemia, which sometimes is difficult to correct even with pharmacologic doses of 1,25-dihydroxycholecalciferol. Under these conditions, when the factors producing bone resorption have been removed and the osteoblastic activity is greatly increased, there is a remarkable flux of Ca into bone due to bone formation. The great uptake of minerals by the skeleton may produce profound hypocalcemia.

Hypercalcemia

Hypercalcemia is an elevation of total serum Ca levels to more than 10.5 mg per dL (when serum protein values are within the normal range). The manifestations of hypercalcemia differ among patients.[94] Mild hypercalcemia may be totally asymptomatic and may be detected during routine blood chemistry tests; however, hypercalcemia may be severe enough to produce lethargy, disorientation, coma, and death.

Clinical Symptoms of Hypercalcemia

Patients with mild hypercalcemia may be totally asymptomatic[66]; however, as serum Ca increases, usually to more than 11.5 mg per dL, numerous symptoms may be present and practically every organ of the body is affected. The most common symptoms are nausea, vomiting, polyuria, polydipsia, lack of concentration, fatigue, somnolence, mental confusion, and even death (Table 73.7).

Renal Effects

Hypercalcemia may cause either an acute and reversible decrement in the GFR or a chronic nephropathy. There are numerous mechanisms by which hypercalcemia decreases the GFR.[287,377,515] Hypercalcemia may lead to vasoconstriction of the afferent arterioles and decreased renal blood flow. It can decrease ultrafiltration across glomerular capillaries. In addition, acute hypercalcemia may produce natriuresis and ECF volume contraction. In chronic hypercalcemic nephropathy, there is a fall in the GFR and a decrease in the maximum urinary concentrating capacity, and the urine is free of cells or casts, although mild proteinuria may be observed. The findings are similar to those seen in patients with interstitial nephritis. The characteristic abnormality of hypercalcemic nephropathy is an inability to concentrate the urine.[40,110,218] This abnormality persists even after the administration of antidiuretic hormone (ADH).[44] The mechanisms by which hypercalcemia impairs concentration of the urine are multiple.[241,422,650] The osmotic gradient of the medulla is decreased, partly because of decreased sodium transport in the thick ascending portion of the loop of Henle. Moreover, hypercalcemia decreases the permeability of the collecting duct to water by inhibiting the adenylate cyclase activity and generation of cAMP in response to ADH. There is some evidence to suggest that increased prostaglandin synthesis may mediate part of this effect. Prostaglandin E_2 (PGE_2) enhances medullary blood flow, inhibits sodium chloride transport in the loop of Henle, and antagonizes the effect of ADH on the collecting duct.[390] It is possible that several of the effects of hypercalcemia on the concentrating mechanism are related to increased prostaglandin synthesis in the medulla. Thus, a salt-wasting nephropathy and the inability to concentrate the urine may explain some of the symptoms such as polyuria and polydipsia seen in patients with hypercalcemia. Chronic persistent hypercalcemia eventually leads to the development of nephrocalcinosis, most commonly localized to the medulla of the kidney.

Gastrointestinal Manifestations

Anorexia, nausea, and vomiting are frequently seen in patients with hypercalcemia. Occasionally, abdominal pain, distention, and ileus may be present.[478] There is an increased incidence of peptic ulcer in patients with primary

73.7 Clinical Manifestations of Hypercalcemia

I. General: apathy, lethargy, weakness
II. Cardiovascular: cardiac arrhythmias, hypertension, vascular calcification
III. Renal: polyuria, hypercalciuria, stones, nephrocalcinosis-impaired concentration of urine renal insufficiency
IV. Gastrointestinal: anorexia, nausea, vomiting, polydipsia, constipation, abdominal pain, gastric ulcer, pancreatitis
V. Neuropsychiatric and muscular: headache, impaired concentration, loss of memory, confusion, hallucination, coma, myalgia, muscle weakness, arthralgia
VI. Heterotopic calcification: band keratopathy, conjunctival irritation, vascular calcification, periarticular calcification

From Slatopolsky E. Pathophysiology of calcium, magnesium, and phosphorus. In: Klahr S, ed. The Kidney and Body Fluids in Health and Disease. New York: Plenum Press; 1983:269, with permission.

hyperparathyroidism, and it has been shown that Ca increases the release of gastrin and hydrochloric acid in the stomach. Moreover, the incidence of pancreatitis is also greatly increased. Several mechanisms have been implicated in the development of pancreatitis. Usually, hypercalcemia increases pancreatic enzyme secretion, and intraductal proteins may cause obstruction of the pancreatic duct. Enhanced conversion of trypsinogen to trypsin due to elevated Ca levels may contribute to the inflammatory process.

Cardiovascular Effects

Calcium has an inotropic effect on the cardiovascular system. Calcium increases peripheral resistance, and hypertension occurs in 20% to 30% of patients with chronic hypercalcemia.[51,131,418] Renal parenchymal damage with elevated levels of renin, increased cardiac output, and severe vasoconstriction may participate in the development of hypertension. The most significant change in the electrocardiogram is a shortening of the QT interval. Because the positive inotropic effect of digitalis is enhanced by Ca, digitalis toxicity may be aggravated by hypercalcemia.

Neurologic and Psychiatric Effects of Hypercalcemia

Patients with hypercalcemia are frequently admitted to psychiatric wards because of nonspecific complaints characterized by lethargy, apathy, depression, and decreased memory. Patients with hypercalcemia secondary to increased PTH levels have electroencephalographic changes that are reversible after removal of the parathyroid adenoma. Moreover, the administration of large doses of PTH to dogs results in increased brain Ca and changes in the electroencephalogram.[25]

Heterotopic Calcification

Patients with hypercalcemia may develop band keratopathy, which is the appearance of corneal calcification. The changes in the cornea are usually permanent. However, conjunctival irritation disappears after correction of the hypercalcemia. Arterial and periarticular calcifications are observed more frequently in patients who have some degree of renal insufficiency,[399] especially those who also have hyperphosphatemia. Vascular calcification has become a critical complication of chronic kidney disease.[120,123,141,398,539] Vascular calcification in CKD associated with the adynamic bone disorder is often associated with hypercalcemia.[147,148,399]

Hypercalcemia

Pathologically, three general mechanisms may lead to the development of hypercalcemia (Table 73.8): (1) increased mobilization of Ca from bone, by far the most common and important mechanism; (2) increased absorption of Ca from the GI tract; and (3) decreased urinary excretion of Ca (of minor importance). In some clinical disorders, although one

73.8 Causes Of Hypercalcemia

I. Hypercalcemia secondary to increased calcium mobilization from bone
  A. Malignancy
    1. Metastatic
    2. Nonmetastatic
      a. Osteoclastic-activating factor
      b. Prostaglandin E_2
      c. Ectopic hyperparathyroidism
  B. Hyperparathyroidism
    1. Primary
      a. Adenoma
      b. Hyperplasia
      c. Neoplastic
    2. Secondary
    3. Multiple endocrine neoplasias
      a. Type I with pituitary and pancreatic tumors
      b. Type II with medullary carcinoma of thyroid and pheochromocytoma
  C. Immobilization
  D. Hyperthyroidism
  E. Vitamin D intoxication
  F. Renal disease
    1. Chronic renal failure
    2. After renal transplantation
    3. Diuretic phase of acute renal failure
  G. Vitamin A intoxication

II. Hypercalcemia secondary to an increase in calcium absorption from the gastrointestinal tract
  A. Sarcoidosis
  B. Vitamin D intoxication
  C. Milk-alkali syndrome

III. Hypercalcemia secondary to a decrease in urinary calcium excretion
  A. Thiazide diuretics
  B. Familial hypocalciuric hypercalcemia

IV. Miscellaneous
  A. Adrenal insufficiency
  B. Tuberculosis
  C. Berylliosis
  D. Dysproteinemias
  E. Hemoconcentration
  F. Hyperalimentation regimens

From Slatopolsky E. Pathophysiology of calcium, magnesium, and phosphorus. In: Klahr S. The Kidney and Body Fluids in Health and Disease. New York: Plenum Press; 1983:269, with permission.

or more of these mechanisms may be operative, compensatory adaptations develop and hypercalcemia may not occur. For example, in idiopathic hypercalciuria due to increased Ca absorption from the GI tract, increased urinary excretion of Ca may prevent the development of hypercalcemia. On the other hand, in hyperparathyroidism, all three mechanisms (increased bone resorption, augmented GI absorption of Ca, and decreased urinary calcium excretion) lead to the development of hypercalcemia.

Hypercalcemia Secondary to Increased Calcium Mobilization from Bone

Hypercalcemia Secondary to Malignancies/Humoral Hypercalcemia of Malignancy

Malignancy is the most common cause of hypercalcemia. Multiple mechanisms underlie the development of hypercalcemia of malignancy, but in general, it is due to a combined disorder of increased mobilization of Ca from the skeleton secondary to increased bone resorption by osteoclasts and variable decreases in the renal excretion of calcium.[74,644] This increased resorption could be due to the action of malignant cells that have metastasized to bone from tumors of such organs as the breast, prostate, kidney, lung, and thyroid.[644] The tumor cells in the bone metastasis produce RANKL and macrophage colony stimulating factor (MCSF) that stimulate production of active osteoclasts and local osteolysis. However, on some occasions, hypercalcemia occurs with no evidence of bone metastasis, and generally, the removal of the tumor results in correction of the hypercalcemia. In these cases, humoral agents are involved. The major humoral osteoclast-stimulating factor is PTH-related peptide (PTHrP).[238,644,720] This factor, which is a endochondral bone morphogen and an endogenous paracrine of the adult mammary glands, oviduct, fibroblasts, and vascular smooth muscle, has sufficient homology with PTH in its amino terminal region to act through PTH receptors on PTH target cells such as the osteoblast and the distal connecting tubule.[277,675,721] Thus, its production by tumors mimics the action of high PTH levels in stimulating bone resorption and renal Ca retention. PTHrP accounts for about 80% of the hypercalcemia associated with malignancies. Other mechanisms of hypercalcemia due to tumors include secretion of PGE_2,[29,145,299,326] especially by solid tumors, the production of TNFα, as in patients with multiple myeloma and lymphosarcoma,[470] and the secretion of IL-1 and TGFβ. The latter factors are often produced in association with PTHrP. TGFα works through epidermal growth factor receptors and stimulates bone resorption. Its production is highly prevalent (40%) in tumors associated with hypercalcemia, and it may play a secondary role in association with many cases in which PTHrP is being produced. In metastatic bone disease, there are usually two effects: (1) an increase in bone resorption and (2) an increase in woven bone formation. If the osteoblastic process (bone formation) predominates, hypercalcemia may not develop. However, if the osteolytic process predominates, the patient develops severe hypercalciuria and hypercalcemia. In contrast to tumors that produce a "parathyroid-like material," the serum phosphorus level or the tubular reabsorption of phosphate usually is not decreased in metastatic bone disease. However, the patient may develop hypophosphatemia when the disease progresses and malnutrition becomes evident. Although many tumors may secrete PTHrP (59 of 72 cases with hypercalcemia)[682] the two most important ones are the epidermoid squamous cell carcinoma of the lung and renal cell carcinoma. Rarely, patients with hypercalcemia of malignancy have elevated levels of circulating immunoreactive PTH.[644,682] Most often this is due to coexistent parathyroid disease and malignancy.[644,682]

Primary Hyperparathyroidism

Primary hyperparathyroidism is the most common endocrine disorder causing hypercalcemia.[65] It is probably the major cause of asymptomatic hypercalcemia in young people and older women. A single adenoma of the parathyroid gland is the most common cause of primary hyperparathyroidism. In contrast, chief cell hyperplasia is commonly observed in patients with secondary hyperparathyroidism caused by renal insufficiency. The incidence of primary hyperparathyroidism increases substantially in both men and women older than 50 years but is two to four times more common in women.[65] The mechanism of hypercalcemia is due to the action of PTH in the skeleton and kidney. The levels of PTH measurable by radioimmunoassay are elevated in primary hyperparathyroidism. The percentage of positive results to confirm the diagnosis depends on the type of antibody used and the sensitivity of each particular radioimmunoassay for PTH. Sensitive assays, using a carboxyterminal antibody, demonstrate elevated levels of PTH in 90% to 95% of patients with primary hyperparathyroidism, but these assays were sensitive to retention of fragments in kidney failure and have been replaced by assays measuring the intact hormone without loss of sensitivity.[65,671] As PTH increases the activity and number of osteoclasts, bone resorption is seen on bone histology. X-ray films of the phalanges show subperiosteal bone resorption. The increased Ca mobilization from bone raises the filtered load of Ca and leads to the development of hypercalciuria despite the effect of PTH in increasing the reabsorption of Ca in the distal nephron. Moreover, the hypercalcemia is aggravated by increased Ca absorption from the gut secondary to high levels of 1,25-dihydroxycholecalciferol in response to high levels of PTH in blood. PTH decreases the renal reabsorption of phosphorus in the proximal and distal tubules, resulting in hypophosphatemia. Patients with primary hyperparathyroidism have a high incidence of peptic ulcer, renal stones, soft tissue calcification, neuromuscular disease, and psychiatric disorders. Because hypercalcemia interferes with the renal countercurrent mechanism responsible for the concentration of the urine, the patient develops polyuria and polydipsia. The treatment of this condition is surgery (parathyroidectomy),

except in mild cases of asymptomatic hypercalcemia (plasma calcium concentration of less than 11 mg per dL), especially in older adults.[66,506,645,705]

Immobilization

Patients who are immobilized for several days develop some degree of hypercalciuria. However, some of these patients may develop hypercalcemia.[51,631] This occurs in diseases involving increased bone turnover such as Paget disease. Hypercalcemia is seen frequently in immobilized patients with multiple fractures. It seems that prolonged periods of immobilization disrupt the balance between bone resorption and formation. The resorptive process predominates because of the depression of osteoblastic activity, and calcium mobilization occurs.

Hyperthyroidism

Serum Ca concentration may increase in thyrotoxicosis. Usually the increment is mild and does not produce severe symptoms. Bone histology reveals an increase in osteoclastic bone resorption and fibroblastic proliferation resembling osteitis fibrosa cystica. Moreover, patients with thyrotoxicosis who present with hypercalcemia usually have low or undetectable levels of PTH in blood.

Vitamin D Intoxication

Vitamin D increases both Ca absorption from the GI tract and bone resorption. Metabolites of vitamin D have been shown to increase the efflux of Ca from bone in vitro. Moreover, administration of 1,25-dihydroxycholecalciferol to dogs fed low Ca diets leads to hypercalcemia, suggesting that the effect on bone was responsible for the rise in extracellular Ca. The manifestations of vitamin D intoxication include high levels of 25-hydroxycholecalciferol in blood, whereas the circulating levels of 1,25-dihydroxycholecalciferol may remain within the normal range. Of course, if a patient receives pharmacologic doses of 1,25-dihydroxycholecalciferol, the hormonal derivative of vitamin D produces toxic effects and the characteristic hypercalcemia.

Renal Disease

Hypercalcemia is rare in patients with chronic kidney failure[620] prior to dialysis. Most patients with renal disease have hypocalcemia, which leads to the development of secondary hyperparathyroidism. Hypercalcemia in patients with end-stage kidney failure receiving treatment is commonly associated with the administration of vitamin D analogs and the adynamic bone disorder.[347] The mechanism of hypercalcemia is both intestinal resorption and excess bone resorption over formation.[280] Extreme hyperplasia of the parathyroid glands may also develop in these patients, and progress to a point at which they no longer respond to normal feedback mechanisms due to the development of clonal adenomatous change.[28] Thus, a greater degree of hypercalcemia may be necessary to suppress PTH secretion by such enlarged glands. In some patients, hypercalcemia may be seen after significant reductions of serum phosphorus levels or after ingestion of large amounts of Ca carbonate usually associated with vitamin D analog treatment.

A mineralization defect described in a substantial number of patients maintained on chronic hemodialysis[620,683] has been shown to be due to aluminum deposition in the interface between osteoid and mineralized bone is responsible for this defect. Many of these patients have mild hypercalcemia and relatively low levels of PTH. This finding has led to the elimination of aluminum from the chronic dialysis environment.

Hypercalcemia occurs more frequently after a successful renal transplantation than in patients with chronic renal insufficiency.[620] Because patients receiving kidney transplants usually have severe secondary hyperparathyroidism, the amount of 1,25-dihydroxycholecalciferol produced by the new kidney, if the graft is successful, is greatly increased due to both high levels of PTH and decreased serum phosphate levels due to the marked phosphaturia after the transplantation. Synergistically, 1,25-dihydroxycholecalciferol and PTH would increase calcium mobilization from bone, leading to hypercalcemia. Obviously, 1,25-dihydroxycholecalciferol also increases Ca absorption from the GI tract. In most patients, the hypercalcemia does not require specific treatment and subsides after 3 to 4 weeks. However, in some patients, specific measures should be taken to prevent nephrocalcinosis, and if the hypercalcemia is severe and persists for several months or years, the patient may require surgical parathyroidectomy.

Vitamin A Intoxication

This is a very rare cause of hypercalcemia and is seen more frequently in children than adults.[132,308,316]

Hypercalcemia Secondary to Increased Calcium Absorption from the Gastrointestinal Tract

There are several clinical entities such as sarcoidosis, vitamin D intoxication, and milk alkali syndrome that are characterized by increased Ca absorption from the gut and positive Ca balance. Some patients also have widespread soft tissue calcification and nephrocalcinosis. Most of these patients have low or undetectable levels of PTH.

Sarcoidosis

About 10% to 20% of patients with sarcoidosis have mild hypercalcemia.[437] This abnormality is secondary to an increase in Ca absorption, and the mechanism responsible for the increased Ca absorption is unregulated production of calcitriol in macrophages of the sarcoid lesions. Serum levels of 1,25-dihydroxycholecalciferol may be elevated in sarcoidosis, but this is not uniform.[38,46] Recent studies in an anephric patient with sarcoidosis with high levels of 1,25-dihydroxycholecalciferol[38] clearly indicate an extrarenal production of 1,25-dihydroxycholecalciferol in sarcoidosis. Adams et al.[7] first demonstrated that alveolar macrophages obtained by bronchial lavage from a patient with sarcoidosis

and hypercalcemia converted 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. In general, patients with sarcoidosis are sensitive to small doses of vitamin D and exposure to ultraviolet radiation of the skin. The administration of corticosteroids in these patients decreases intestinal calcium absorption and corrects the hypercalcemia. Hypercalcemia also has been demonstrated in patients with histoplasmosis,[681] tuberculosis,[6] disseminated coccidioidomycosis,[361] and berylliosis,[646] all due to unregulated calcitriol production by macrophages associated with disease lesions.

Vitamin D Intoxication

Vitamin D and its metabolites, especially 1,25-dihydroxycholecalciferol, increase intestinal Ca absorption. Thus, high concentrations of vitamin D metabolites (mainly 25-hydroxycholecalciferol) in blood are responsible for the hypercalcemia observed in vitamin D intoxication. As described already, vitamin D metabolites may also have a direct effect on bone resorption, which contributes to the development of hypercalcemia.

Milk Alkali Syndrome

This syndrome was seen frequently in patients with peptic ulcer disease who ingested large amounts of Na and Ca bicarbonate.[444,491] Calcium carbonate contains 40% of elemental Ca. Some patients who ingested up to 20 g of Ca carbonate in 24 hours developed severe hypercalcemia. Moreover, alkalosis increases renal Ca reabsorption in the distal tubule and reduces bone turnover, thus decreasing Ca uptake by bone.

Hypercalcemia Secondary to Decreased Urinary Calcium Excretion

The decrease in urinary excretion of Ca may be secondary to a fall in the filtered load of Ca or to an increase in the tubular reabsorption of Ca. The fall in the filtered load of Ca may be secondary to a decrease in serum Ca level or the GFR. By definition, if the patient has a disorder that produces hypocalcemia with a decrease in urinary Ca excretion, he or she cannot be at the same time hypercalcemic; thus, such disorders can be excluded. A fall in the GFR may decrease Ca delivery to the distal tubule, and less Ca may be excreted in the urine. This situation, which may occur in profound dehydration, is self-limited and the hypercalcemia does not persist for a prolonged time. Moreover, dehydration or other conditions that decrease GFR may also modify the transport of Na and water and affect the reabsorption of Ca by the nephron.

Thiazide Diuretics

Patients taking thiazide diuretics may develop moderate hypercalcemia.[93,420,497,514] The mechanisms for the hypercalcemia are not fully understood, and a number of factors are involved. Thiazides decrease urinary excretion of Ca by increasing Ca resorption in the distal tubule. This reduction in urinary Ca seems to require some degree of ECF volume contraction and the presence of PTH, because patients with hypoparathyroidism do not greatly reduce the amount of Ca in the urine after the administration of thiazides. Thus, in patients with increased Ca mobilization from bone, the administration of thiazides may blunt the expected hypercalciuria and potentially raise serum Ca. However, thiazides also have a direct effect on the skeleton.[420] Administration of thiazides intravenously produces a mild change in ionized Ca. This effect is apparently potentiated by PTH because the effect is greater in patients with hyperparathyroidism than in healthy subjects.[514] Finally, there is controversy about whether thiazides per se increase the release of PTH. Most of the evidence indicates that this is not the case.

Familial Hypocalciuric Hypercalcemia and Neonatal Severe Hyperparathyroidism

Marx et al.[427,428] describe a syndrome characterized by hypocalciuria and mild hypercalcemia. Usually several members of the same family are affected. Familial hypocalciuric hypercalcemia is characterized by autosomal dominant transmission and generally follows a benign course. Some patients may have a mild degree of hyperparathyroidism; however, the hypercalcemia persists after subtotal parathyroidectomy. The main characteristic of this syndrome is a decrease in urinary Ca. Thus, the calcium:creatinine ratio provides an important diagnostic tool to differentiate familial hypocalciuric hypercalcemia from primary hyperparathyroidism. The development of hypercalcemia in young members of the family also favors this diagnosis. The pathogenesis of this syndrome is due to mutations in the Ca sensor of the parathyroid gland chief cells and the TAL/distal nephron epithelia or to autoantibodies.[96,493,548] As a result, these cells do not downregulate PTH secretion and Ca transport with the correct sensitivity to the plasma calcium. Mutations in the Ca sensor are also responsible for neonatal primary hyperparathyroidism. Two abnormal alleles for calcium sensor mutations produce the primary hyperparathyroidism, whereas single abnormal alleles produce familial hypocalciuric hypercalcemia.[512]

Treatment of Disorders of Calcium Metabolism

Hypocalcemia

The treatment of severe hypocalcemia and tetany is a medical emergency. Administration of Ca intravenously is mandatory to prevent severe complications and even death in these patients. If the patient has severe hypocalcemia and tetany in the absence of hypomagnesemia, the symptoms can be easily relieved by administration of 1 or 2 ampules of Ca gluconate given intravenously over 10 minutes (1 ampule of Ca gluconate has approximately 100 mg of elemental Ca). This initial treatment can be followed by administration of 1.0 g of elemental Ca dissolved in 500 mL of dextrose in water and given intravenously over 4 to 6 hours. If the condition responsible for the hypocalcemia cannot be corrected (e.g., hypoparathyroidism), a program for the chronic treatment

of hypocalcemia should be instituted. The amount of Ca in the diet should be supplemented by 1 to 3 g of elemental Ca. Calcium carbonate has roughly 40% of elemental Ca; commercial preparations such as 3M Titralac or Os-Cal can be used in this situation. However, in many circumstances, administration of large amounts of Ca may not be sufficient to increase absorption by the intestine; therefore, different metabolites of vitamin D should be used. In chronic situations, 1,25-dihydroxycholecalciferol could be used. The dosage used ranges from 0.5 to 2 μg per 24 hours. Most patients eventually require 0.5 μg per day. If this metabolite of vitamin D is not available, vitamin D_2 or D_3, about 50,000 U three times a week, could be used instead. The dosage can be gradually increased up to 50,000 to 100,000 units daily. The serum Ca should be carefully monitored to prevent severe hypercalcemia, nephrocalcinosis, and potentially irreversible renal disease.

Hypercalcemia

A useful maneuver to correct hypercalcemia is to increase urinary Ca excretion (Table 73.9).[469] As discussed previously, only 1% to 2% of the filtered load of Ca is excreted by the kidney. This percentage can be greatly increased, and the kidney may thus become an excellent excretory organ for Ca. Because most patients with hypercalcemia develop dehydration and volume contraction with a consequent decrease in GFR, one of the first therapeutic maneuvers is the expansion of the ECF space. Expansion with saline requires several liters per day; therefore, it is mandatory that strict records be kept to maintain accurate determination of the intake and output of fluids. In most patients, it is convenient to determine the central venous pressure (CVP), which will allow volume expansion and prevent the potential risk of overexpansion and heart failure. Thus, after a CVP line is inserted, volume expansion with saline should be instituted until the venous pressure increases to 10 to 14 mm Hg. This maneuver alone will increase the GFR and decrease the reabsorption of Ca in the proximal tubule and in the ascending portion of the loop of Henle. Thus, fractional excretion of Ca will be greatly increased. This effect can be enhanced by administration of diuretics such as furosemide, bumetanide, or ethacrynic acid. The administration of 40 to 120 mg of furosemide every 4 hours is recommended in most patients. Using these maneuvers, fractional excretion of Ca can be increased to 10% of the filtered load. Thus, 1 g of Ca can be easily excreted in the urine in 24 hours. The administration of large amounts of saline and diuretics usually increases the excretion of potassium. To prevent arrhythmias, serum potassium should be maintained between 3.5 and 5.0 mEq per L. This can be achieved by adding 10 to 30 mEq of potassium to each liter of saline.

Although expansion of the ECF may control the hypercalcemia, this effect is temporary, and because in most circumstances, hypercalcemia is secondary to increased mobilization of Ca from bone, the physician may be forced to add a second line of medications to decrease the efflux of Ca from bone. In addition, many patients with hypercalcemia have renal failure and are not responsive to diuretics.

Bisphosphonates

A derivative of the bisphosphonates, disodium dichloroethylene diphosphonate,[618] was originally used with success on an experimental basis in patients with tumors and bone metastases and severe hypercalcemia.[616] Pamidronate, ibandronate, and zoledronic acid, second- and third-generation bisphosphonates, respectively, have become the standard of therapy for hypercalcemia of malignancy[39,49,71,239,576] and other causes of hypercalcemia requiring inhibition of bone resorption. One or two doses of 30 to 60 mg of pamidronate or a single dose of zoledronic acid intravenously are usually effective.[24] Potent bisphosphonates, including alendronate and risedronate, have become available and are effective as oral agents for hypercalcemia. Renal toxicity has to be considered when using these agents.[554]

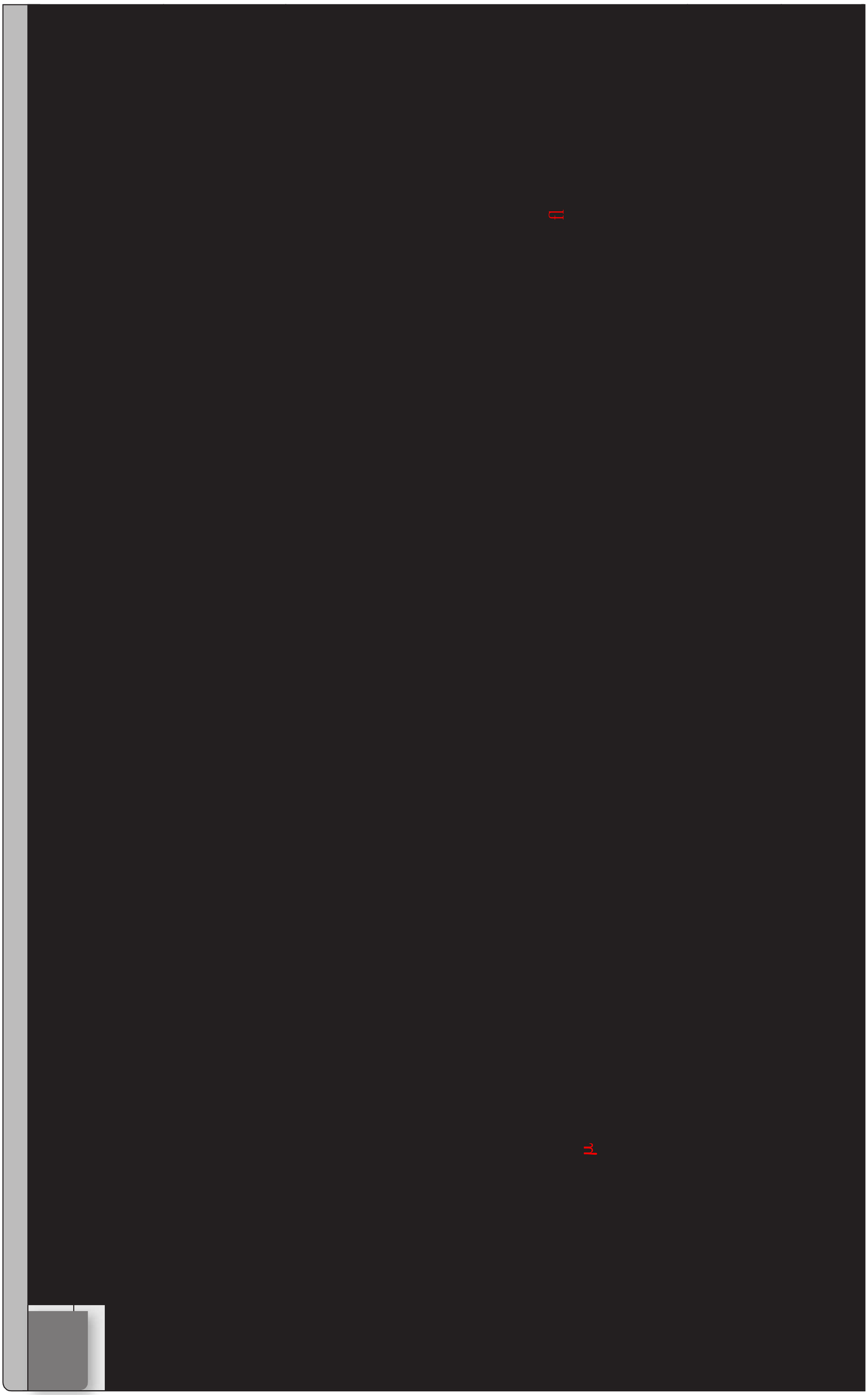
Cinacalcet

Cinacalcet maintains long-term normocalcemia in patients with mild or asymptomatic primary hyperparathyroidism.[506] Cinacalcet is an orally bioavailable calcimimetic that increases the sensitivity of Ca sensing receptors to extracellular calcium. Cinacalcet in doses of 30 to 50 mg twice daily is sufficient to normalize serum Ca in hyperparathyroidism. Cinacalcet is also used in the treatment of secondary hyperparathyroidism seen in CKD.[457]

Calcitonin produces hypocalcemia by decreasing the activity of osteoclasts. The dose commonly used ranges from 2 to 5 MRC U per kg of body weight every 6 to 12 hours. The degree of hypocalcemia produced by this drug is mild, and the decrease is usually 1 to 3 mg per dL.[311] Calcitonin can be given either intramuscularly or intravenously in a concentration of 5 MRC U per kg dissolved in 500 mL of 5% dextrose in water to be given over 6 hours. Calcitonin is also available as a nasal spray. Unfortunately, in most patients, there is an escape from the hypocalcemic effect of calcitonin after 6 to 10 days of administration.

Miscellaneous Approaches

Mithramycin is an antibiotic originally introduced for the treatment of testicular tumors. Mithramycin blocks the activity of osteoclasts and may result in severe hypocalcemia.[615,617] It is usually given intravenously over 3 to 4 hours in a dose of 25 μg per kg of body weight dissolved in 500 mL of 5% dextrose in water or saline. Mithramycin is an effective drug. However, the effects may be seen only after 48 to 72 hours. One of the toxic effects of the drug is severe thrombocytopenia and bleeding. In general, the drug should not be given more than once every 4 or 5 days, and its use has been almost eliminated by development of effective, less toxic agents such as the bisphosphonates.[616]



There are rare tumors that produce prostaglandins that have resulted in the development of hypercalcemia. The use of aspirin in a dosage of 1 g four times daily or indomethacin 75 mg twice daily has ameliorated the hypercalcemia.[89,296,589]

If hypercalcemia is mainly due to increased absorption of Ca from the GI tract, such as in sarcoidosis, it is obviously important to decrease the amount of Ca in the diet and to administer corticosteroids, which will result in decreased absorption.[471,715] Usually prednisone (20 mg twice daily) has been effective in conditions such as sarcoidosis, which is characterized by increased 1,25-dihydroxycholecalciferol production by macrophages in the granulomas. The dose of corticosteroid should be titrated down to the lowest dose required to maintain normocalcemia.

Phosphate has been used in the treatment of hypercalcemia.[433] However, the presence of a normal or slightly elevated serum phosphorus level or decreased renal function precludes the use of this medication. Phosphorus should be given only when the serum phosphorus level is low, and its use is generally discouraged. If an elevation of the serum phosphorus level is achieved and the serum Ca level decreases, the patient may deposit Ca phosphate in soft tissues.

There are some general measures that are important in the treatment of hypercalcemia. Immobilization should be avoided as much as possible, especially in patients with rapid bone turnover such as those with Paget disease. Because most patients with hypercalcemia have an underlying tumor that is causing the hypercalcemia, physicians should be aware of this pathogenetic mechanism and join efforts with oncologists in the diagnosis and treatment of the malignancy. Finally, when the hypercalcemia is very severe and the patient has advanced renal insufficiency, acute hemodialysis is an effective method of correcting the hypercalcemia (Table 73.9).

MAGNESIUM

General Considerations

Magnesium is the second most abundant intracellular cation (after potassium) and the fourth most abundant cation of the body (after Ca, K, Na). Magnesium (Mg^{2+}) is divalent and has an atomic weight of 24. Mg^{2+} has an essential role as a cofactor for various enzymes, most of which use ATP. Mg^{2+} increases the stimulus threshold in nerve fibers and in pharmacologic doses has a curare-like action on neuromuscular function, probably inhibiting the release of acetylcholine at the neuromuscular junction. Mg^{2+} decreases peripheral resistance and lowers blood pressure. Like Ca^{2+}, Mg^{2+} plays a role in the regulation of PTH secretion. Hypermagnesemia suppresses the release of PTH. Acute hypomagnesemia has the opposite effect; however, profound magnesium depletion decreases the release of PTH. In vitro, magnesium increases the solubility of both calcium and phosphorus.

Body Stores of Magnesium

The total body magnesium concentration is approximately 2,000 mEq, or 25 g. As with calcium, only a small fraction (about 1%) of the body magnesium is present in the ECF compartment. Approximately 60% of the total body magnesium is found in bone. Most of the magnesium in bone is associated with apatite crystals, and a significant amount is present as a surface-limited ion on the bone crystal and is freely exchangeable. Approximately 20% of the total body magnesium is localized in the muscle. The remaining 20% is localized in other tissues of the body; the liver has a high magnesium content. The concentration of magnesium in blood is maintained within narrow limits, ranging between 1.5 and 1.9 mEq per L. Approximately 75% to 80% of the magnesium in serum is ultrafiltrable, and the rest is protein bound.[99,432] Most of the ultrafiltrable magnesium is present in the ionized form. Red cell magnesium concentration is approximately 5 mEq per L.

Intracellular free Mg^{2+} levels in renal tubular cells are in the range of 500 μmol per L.[380] High-performance liquid chromatography and fluorescent methods have been used to ascertain intracellular Mg^{2+} levels. Mitochondrial inhibitors that deplete intracellular ATP produce modest increases in intracellular Mg^{2+} and Ca^{2+}. The effects of these inhibitors are due to the changes in ATP levels.[380] Another agent, antimycin, diminishes ATP levels and decreases intracellular Mg^{2+} to 430 μmol per L but increases cytosolic Ca^{2+}, indicating that Mg^{2+} movements can be distinguished from those of Ca^{2+} by fluorescent techniques. Also, these studies indicate that intracellular regulation of Mg^{2+} is distinctive from that of Ca^{2+}. The role of intracellular Mg^{2+} in the control of cell function remains poorly understood.[160] However, intracellular Mg^{2+} levels are rapidly changed through a number of different influences that have important effects on cell function.

Magnesium Balance

Approximately 300 mg, or 25 mEq, of magnesium is ingested daily in the diet (1 mEq = 12 mg). A large portion of dietary magnesium is provided by the ingestion of green vegetables. A minimal magnesium intake of 0.3 mEq per kg of body weight is apparently necessary to maintain magnesium balance in the average person. Of the total amount of magnesium ingested in the diet, about one third is eliminated in urine and the rest in feces (Fig. 73.18). Thus, on a normal diet containing approximately 300 mg of magnesium, 30% to 40% of the ingested magnesium is absorbed (Fig. 73.18). Small amounts of magnesium, on the order of 15 to 30 mg per day, are secreted by the GI tract. Many studies have shown that animals fed low-magnesium diets can excrete urine that is very low in magnesium.[99,160,173] However, the GI tract continues to secrete small amounts of magnesium, and the animal becomes magnesium depleted. Most of the magnesium is absorbed in the upper GI tract. Magnesium shares with calcium similar pathways for absorption in

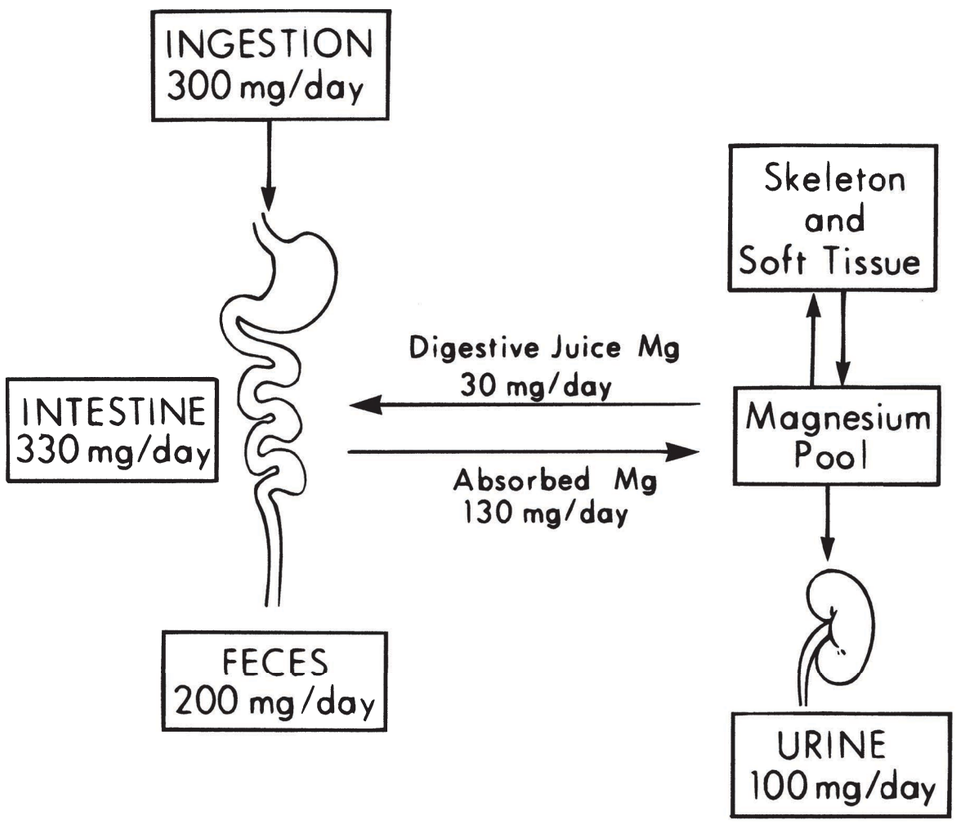


FIGURE 73.18 Diagrammatic representation of magnesium metabolism in humans showing the contribution of the gastrointestinal tract, the kidney, bone, and soft tissues to the magnesium pool. (From Slatopolsky E, Rosenbaum R, Mennes P, et al. The hypocalcemia of magnesium depletion. In: Massry S, Ritz E, Rapado A, eds. *Homeostasis of Phosphate and Other Minerals*. New York: Plenum; 1978:263.)

the intestine, but whereas most of the evidence suggests that calcium is actively absorbed from the GI tract, magnesium is absorbed mainly by ionic diffusion and "solvent drag" resulting from the bulk flow of water. A carrier mechanism also may be involved in this process.[12,235] Intestinal magnesium absorption occurs via two different pathways: a nonsaturable paracellular passive transport and a saturable active transport. At low intraluminal concentrations, magnesium is absorbed primarily via the active cellular route, and with increasing concentrations, via the paracellular pathway. In hypomagnesemia with secondary hypocalcemia, all magnesium is absorbed via the paracellular pathway. This is evidenced by mutations in TRPM6 which leads to disruption of transcellular magnesium absorption in the intestine and kidney.[338] The factors controlling the absorption of magnesium from the bowel are not fully understood. Although there is some evidence to suggest that vitamin D may influence the absorption of magnesium, this role seems to be less important for magnesium than for the absorption of calcium.[446,449] It is known that patients with severe renal insufficiency and low levels of 1,25-dihydroxycholecalciferol may develop profound hypermagnesemia by slightly increasing the amount of magnesium in the diet without modifying the metabolites of vitamin D in serum. The sigmoid colon has the capability of absorbing magnesium, and there are several reports in the literature of patients who developed magnesium toxicity after receiving enemas containing magnesium; most of these patients also had renal insufficiency. Experimental evidence in different species suggests an interrelationship between magnesium and calcium absorption from the GI tract. Diets high in calcium decrease the absorption of magnesium, and diets low in magnesium increase the absorption of calcium.

Renal Handling of Magnesium

Approximately 2 g of magnesium is filtered daily by the kidney, and about 100 mg appears in the urine. Thus, 95% to 97% of the filtered load of magnesium is reabsorbed, and 1% to 3% is excreted in the urine (Fig. 73.19).[159,160] In states of magnesium deficiency, the kidney can reduce the amount of magnesium excreted in the urine to less than 0.5% of the filtered load. On the other hand, during magnesium infusion or in patients with far-advanced renal insufficiency, as is commonly seen, the kidney can excrete 40% to 80% of the filtered load of magnesium.[641] The proximal tubule is poorly permeable to magnesium,[98,99,159,257,641,718] and probably no more than 15% to 20% is reabsorbed in this segment (Fig. 73.19). This is in contrast to the amount of sodium and calcium (60%) reabsorbed in this segment of the nephron. The tubular fluid magnesium is usually 1.5-fold greater than the plasma magnesium,[12] and it increases along perfused tubules in a linear manner, with net water reabsorption. Further studies indicated a low level of backflux from peritubular membrane into the lumen.[528,608] In the descending limb of the loop of Henle, the magnesium concentration is raised severalfold over the ultrafiltrable serum concentration due to water removal. The TAL of the loop of Henle seems to play a critical role in the reabsorption of magnesium. Early studies by LeGrimellec et al.[362] and by Morel et al.[461] demonstrated that the loop of Henle was the major site for magnesium reabsorption. Approximately 60% to 70% of the filtered magnesium was reabsorbed between the last accessible portion of the proximal tubule and the early distal tubule (Fig. 73.19).[534] In the presence of a normal plasma magnesium concentration, magnesium absorption increases with intraluminal magnesium concentration, without indication of a T_{max} for magnesium. On the other hand, an increase in plasma magnesium concentration (i.e., on the basolateral membrane) resulted in a significant depression of magnesium absorption, suggesting that hypermagnesemia decreases magnesium absorption in the loop of Henle by inhibiting magnesium transport at the basolateral membrane. Thus, the permeability of the TAL to magnesium is quite different from that of the proximal tubule. Two mechanisms have been proposed to explain magnesium transport in the TAL of the loop of Henle: (1) passive,[81] secondary to the potential difference generated by the active transport of sodium chloride, which facilitates paracellular movement of Mg^{2+}; and (2) active,[292,552,593] because the chemical concentration of magnesium in the cells is higher than that in the lumen, and the potential gradient may not be great enough to explain the entry of magnesium into cells. Diets deficient in magnesium or the administration of PTH enhances the reabsorption of magnesium in the TAL of the loop of Henle. On the other hand, diets containing large amounts of magnesium or factors that decrease the reabsorption of sodium chloride in this portion of the nephron (ECF volume

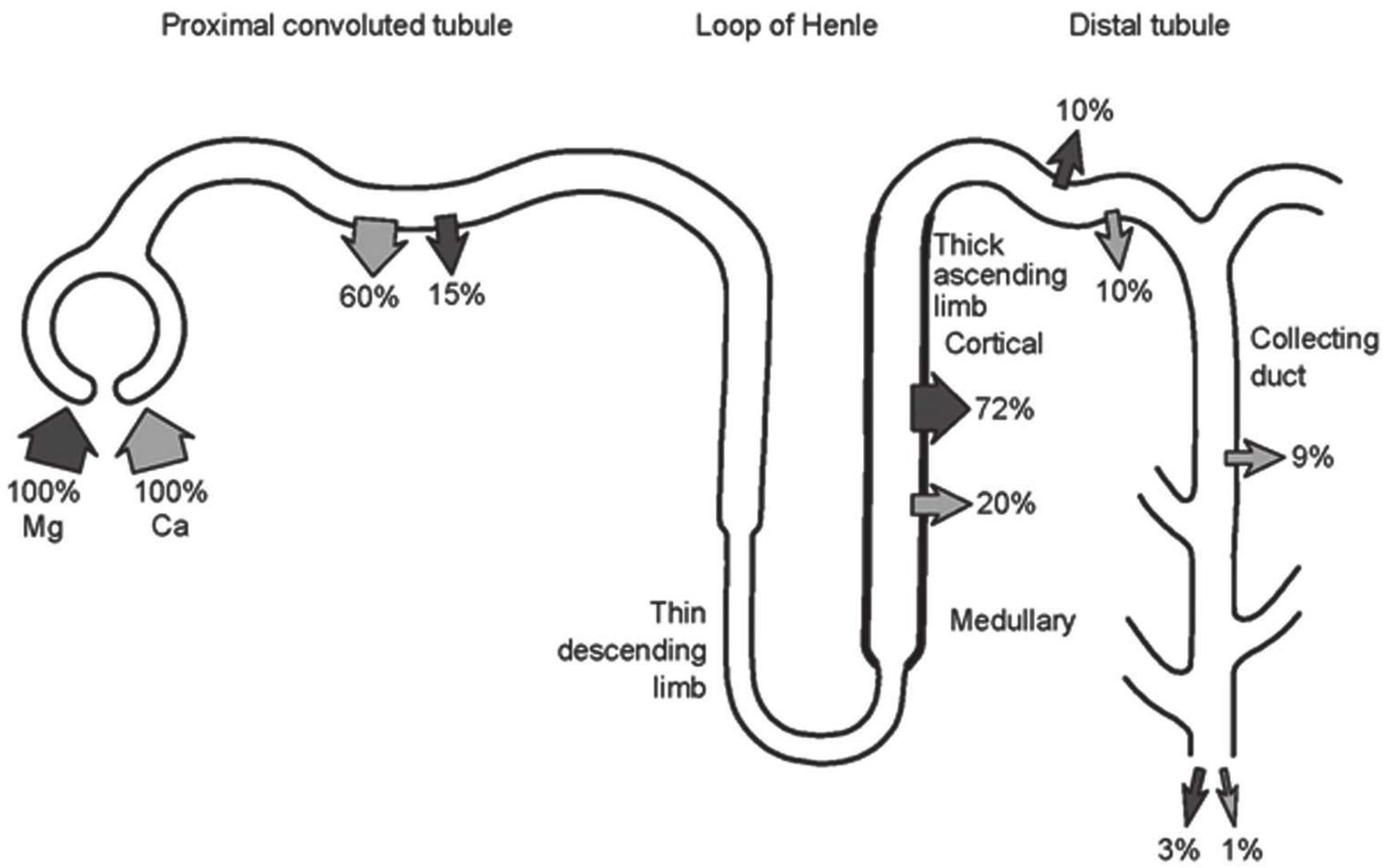


FIGURE 73.19 Summary of segmental magnesium absorption along the nephron relative to sodium and calcium reabsorption. (From Quamme GA, De Rouffignac C. Renal magnesium handling. In Selding D, Giebisch G, eds. *The Kidney*. New York: Lippincott Williams & Wilkins; 2004:1711.)

expansion, administration of diuretics such as furosemide, bumetanide, or ethacrynic acid) also decrease the reabsorption of magnesium.

Hypomagnesemia with Hypercalciuria and Nephrocalcinosis

Recently a protein, paracellin 1 (PCLN1), was detected in the TAL and in the distal tubule.[613] PCLN1 or claudin16 is a member of the claudin family of high-junction proteins. PCLN1 is a highly negative-charged protein, with 10 negatively charged residues and a net charge of −5 (Fig. 73.20).[613] Mutations in the protein induce renal Mg^{2+} wasting, hypercalciuria, nephrocalcinosis, and renal failure. PCLN1 plays an important role in the conductance of the TAL. The negative charges may contribute to the cationic selectivity of the paracellular pathway for the reabsorption of calcium and magnesium.[613]

The terminal segment of the nephron (late distal tubule and collecting duct) appears to play a minor role in the reabsorption of magnesium under normal conditions.[527,532,534] However, more recent studies by the same investigators indicate that the distal tubule also plays an important role in magnesium conservation.[531] The distal tubule normally reabsorbs about 10% of the filtered load of magnesium. Because there is little reabsorption of magnesium in the collecting duct, the distal tubule plays a key role in determining the final urinary excretion of magnesium.

Recent studies with immortalized DCT cell lines have shown that magnesium uptake is specific and regulated by factors shown to influence distal magnesium reabsorption. Quamme and DeRouffignac[533] speculated that Mg^{2+} entry is through a channel, and transport is dependent on the transmembrane voltage. The active step is at the basolateral membrane where Mg^{2+} leaves the cell against both electrical and concentration gradient. Na^{+}–Mg^{2+} exchange may occur, with Na^{+} moving back into the cell, coupled with Mg^{++} exiting from the cell into the interstitium. A large number

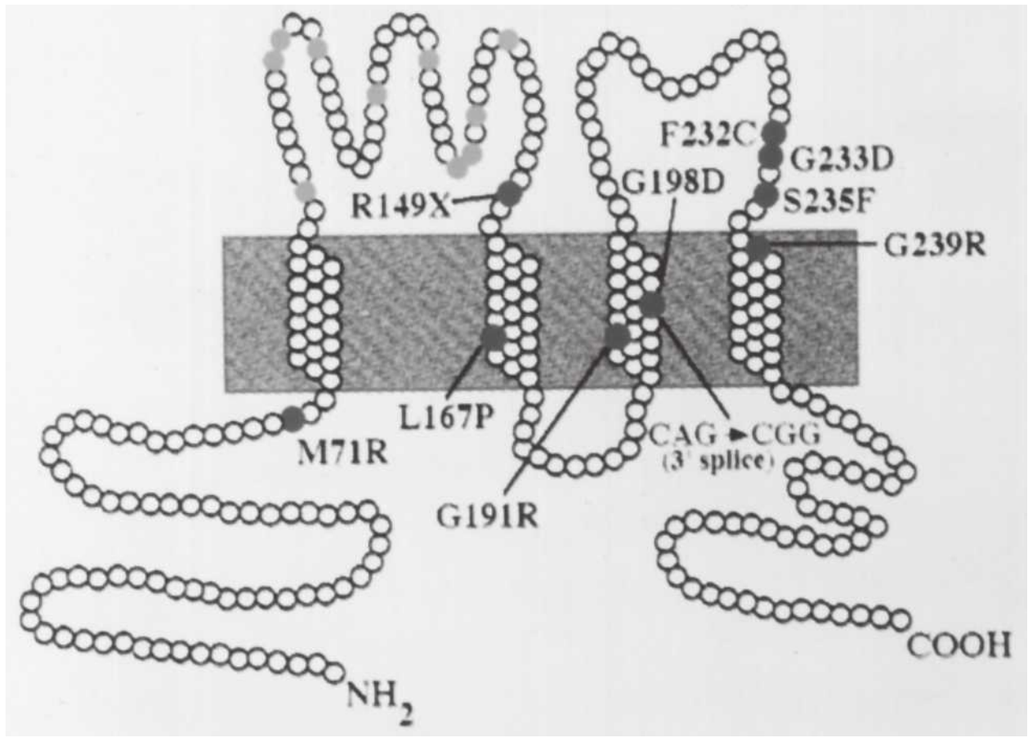


FIGURE 73.20 Structure of the *PCLN-1* human gene. The red dots indicate mutations in *PCLN-1* in patients with recessive renal hypomagnesemia. (From Simon DB, Lu Y, Cahote KA, et al. Paracellin-1, a renal tight junction protein required for paracellular Mg^{2+} resorption. *Science*. 1999;285:103.)

of hormones, such as PTH, calcitonin, glucagon, and vasopressin, stimulate Mg^{2+} reabsorption in the thick ascending loop and distal tubule; however, they have no effect in the proximal tubule.

Chronic administration of mineralocorticoids increases magnesium excretion. Several interrelationships between calcium and magnesium reabsorption have been demonstrated. The administration of one of these two elements decreases the reabsorption of the other. When large amounts of magnesium are given intravenously, there is a remarkable decrease in the renal reabsorption of calcium and vice versa. Alcohol also affects the handling of magnesium by the kidney. A remarkable short-lived hypermagnesuria is seen after alcohol is given to experimental animals or humans. The intravenous administration of glucose has a similar effect.

In summary, in contrast to calcium, the thick ascending portion of the loop of Henle is the most important portion of the nephron in the regulation of magnesium reabsorption. Magnesium reabsorption in the loop occurs within the cortical TAL primarily by passive means driven by the transepithelial voltage through the paracellular pathway. On the other hand, magnesium reabsorption in the distal tubule is transcellular and active in nature. Moreover, the reabsorption of magnesium in the proximal tubule, in contrast to that of sodium, calcium, and phosphate, is rather limited.

Hypermagnesemia

By far the most common cause of hypermagnesemia is chronic renal insufficiency.[542] The kidney can excrete large amounts of magnesium in the urine. Thus, hypermagnesemia is seldom seen in patients with normal renal function, even if the patient ingests large amounts of magnesium such as antacids containing magnesium or laxatives such as milk of magnesia. Mild hypermagnesemia may be seen in patients with GFRs of approximately 10 mL per minute. However, moderate hypermagnesemia is usually seen in patients with GFRs of less than 5 mL per minute. As renal insufficiency progresses, the fractional excretion of magnesium in the urine significantly increases. Patients with a GFR of 120 mL per minute excrete approximately 5% of the filtered load of magnesium. However, patients with far-advanced renal failure (GFR of less than 10 mL per minute) may excrete up to 40% to 80% of the filtered load of magnesium.[542] Thus, patients with chronic renal failure may not be able to increase magnesium excretion further after ingestion of large amounts of magnesium. Therefore, if magnesium ingestion is increased (after administration of laxatives or antacids containing magnesium) in patients with advanced renal failure, profound hypermagnesemia and death may occur. In obstetric wards, magnesium is still used for the treatment of eclampsia.[523] In some of these patients, the GFR is decreased, and the administration of large amounts of magnesium sulfate may result in hypermagnesemia. Although most of the magnesium is absorbed in the small intestine, the sigmoid colon can also absorb magnesium. Healthy subjects receiving large amounts of magnesium sulfate per rectum have been found to have serum magnesium levels of more than 10 mEq per L.[164]

Symptoms and Signs of Hypermagnesemia

Profound hypermagnesemia blocks neuromuscular transmission and depresses the conduction system of the heart. The neuromuscular effects of magnesium are antagonized by the administration of calcium. Mild hypermagnesemia is well tolerated. However, if serum magnesium levels increase to 5 to 6 mg per dL, there may be a decrease in tendon reflexes[706] and some degree of mental confusion. If the serum magnesium level increases to 7 to 9 mg per dL, the respiratory rate slows and the blood pressure falls. If serum magnesium levels increase to about 10 to 13 mg per dL, there is usually profound hypotension and severe mental depression. When the levels increase further to about 15 mg per dL, death may occur.[17,164,706] In uremic patients, the adverse effect of hypermagnesemia may be worsened by the presence of hypocalcemia. Acute hypermagnesemia may also produce mild hypocalcemia. This may be due to (1) suppression of the release of PTH and (2) competition for tubular reabsorption between calcium and magnesium, leading to decreased calcium reabsorption and hypercalciuria, which aggravates the hypocalcemia produced by decreased release of PTH. In chronic renal insufficiency, there is probably an increase in red cell magnesium and muscle magnesium, but the results are controversial. The amount of magnesium in bone is apparently increased in cortical and trabecular bone.[17]

Hypomagnesemia

Hypomagnesemia is defined as a decrease in serum magnesium to levels less than 1.5 mg per dL. Diseases involving the small intestine may decrease magnesium absorption and are the most common cause of hypomagnesemia (Table 73.10). It is difficult to predict the degree of total body magnesium deficiency by determining only serum magnesium concentration. Because only 1% of magnesium is present in the ECF compartment, changes in intracellular magnesium and skeletal magnesium can modify the concentration of serum magnesium, and it may not be possible to assess precisely the degree of magnesium deficiency by determining serum magnesium level. Probably the determination of skeletal or muscle magnesium may provide a better index of magnesium deficiency. However, these determinations are not practical in clinical medicine. In patients with magnesium deficiency, the administration of 50 to 100 mEq of magnesium per day usually corrects the hypomagnesemia after a short time. Magnesium depletion can also produce changes in other electrolytes. Usually there is an increase in potassium excretion in the urine, and patients may develop hypokalemia.[710] In several experimental studies, it has been shown in humans[599] and animals[711] that magnesium depletion is accompanied by urinary potassium losses. Potassium alone did not increase muscle potassium unless

73.10 Causes of Hypomagnesemia

I. Decreased intestinal absorption
   A. Severe diarrhea
   B. Intestinal bypass
   C. Surgical resection
   D. Tropical and nontropical sprue
   E. Celiac disease
   F. Invasive and infiltrative process; lymphomas
   G. Prolonged gastrointestinal suction

II. Decreased intake
   A. Starvation
   B. Protein energy malnutrition
   C. Chronic alcoholism
   D. Prolonged therapy with intravenous fluids lacking magnesium

III. Excessive urinary losses
   A. Diuretic phase of acute tubular necrosis
   B. Postobstructive diuresis
   C. Diuretic therapy
   D. Diabetic ketoacidosis (during treatment)
   E. Chronic alcoholism
   F. Hypercalcemic states
   G. Primary aldosteronism
   H. Inappropriate antidiuretic hormone secretion
   I. Aminoglycoside toxicity
   J. Idiopathic renal magnesium wasting
   K. Cisplatinum
   L. Cyclosporine
   M. Gitelman syndrome

From Slatopolsky E. Pathophysiology of calcium, magnesium, and phosphorus. In: Klahr S, ed. The Kidney and Body Fluids in Health and Disease. New York: Plenum Press; 1983:269, with permission.

magnesium replacement was given as well to patients receiving diuretics.[177] It has been suggested that the effect of magnesium on intracellular potassium is a result of magnesium stimulating Na-K-ATPase activity, allowing the cell to maintain a potassium gradient.[588] However, the most important manifestation of hypomagnesemia is the development of hypocalcemia and tetany. Experimental animals fed a low-magnesium diet develop hypocalcemia.[125,175,348,450] However, the rat becomes hypercalcemic. The pathogenesis of hypocalcemia in magnesium depletion is multifactorial. Hypomagnesemia has profound effects on PTH metabolism and bone physiology. It is known that mild hypomagnesemia increases acutely the levels of PTH in vivo[101] or in vitro[247]; on the other hand, profound hypomagnesemia decreases the levels of PTH in blood.[21] It seems that neither the biosynthesis nor the conversion of pro-PTH to PTH is greatly affected by the concentration of magnesium.[248,251] However, the release of PTH is influenced by the serum magnesium concentration.[20] Several investigators have demonstrated that the administration of magnesium to patients with severe hypomagnesemia who have low levels of immunoreactive PTH in serum increases the release of PTH a few minutes after magnesium administration. Also, there is evidence to indicate that during hypomagnesemia, the skeleton is resistant to the action of PTH,[136,567] and in general, the administration of mildly pharmacologic doses of PTH does not elicit a normal calcemic response in patients with magnesium depletion. Studies by Freitag et al.[194] have further clarified this abnormality. The uptake of PTH by bones obtained from dogs with experimental magnesium depletion was greatly diminished, and the release of cAMP by bone was also blunted in hypomagnesemia. In addition to a decrease in the release of PTH and skeletal resistance to this hormone, in magnesium depletion there is evidence that the ionic exchange from the hydration shell of bone between calcium and magnesium also is decreased[412]; thus, on a physicochemical basis, less calcium is mobilized from bone in hypomagnesemia. Thus, the decrease in the release of PTH, the low uptake of PTH by bone, and the decreased heteroionic exchange of calcium for magnesium in bone are all pathogenetic factors responsible for the hypocalcemia observed in patients with profound magnesium depletion.

Clinical Manifestations of Hypomagnesemia

Patients with severe hypomagnesemia usually develop some degree of anorexia, mental confusion, and vomiting. In general, there is increased neuromuscular irritability, and tremors and seizures are usually observed in these patients. Muscle fasciculation and positive Trousseau's and Chvostek's signs can be observed. Nodal or sinus tachycardia and premature atrial or ventricular contractions may occur. The electrocardiogram may show prolongation of the QT interval and broadening and flattening or even inversion of the T waves. Magnesium deficiency potentiates the action of digitalis, and there is an enhanced sensitivity to the toxic effects of digitalis. Because magnesium plays a key role in regulating the activity of Na-K-ATPase, which is the enzyme responsible for the maintenance of intracellular potassium concentration, severe alterations in skeletal muscle and myocardial function are observed. Sometimes it is difficult to decide whether the changes in the electrocardiogram are related to magnesium or potassium depletion. Most of these patients also have profound hypocalcemia, and sometimes it is difficult to determine whether the symptoms are due to magnesium deficiency or to the concomitant hypocalcemia. Other neurologic manifestations may include vertigo, ataxia, nystagmus, and dysarthria. Changes in personality, depression, and sometimes hallucinations and psychosis have been observed. Patients also may show some degree of hypophosphatemia. In the rat, it has been shown that magnesium deficiency promotes renal phosphate excretion.[342]

Mechanisms Responsible for the Development of Hypomagnesemia

From the pathogenetic point of view, three main mechanisms are responsible for the development of hypomagnesemia: (1) decreased intestinal absorption, (2) decreased intake, and (3) excessive urinary losses.

Hypomagnesemia Secondary to Decreased Intestinal Absorption of Magnesium

By far the most common causes responsible for the development of hypomagnesemia are pathologic entities affecting the small bowel. In these conditions, the kidney adapts to the hypomagnesemia and decreases the urinary excretion of magnesium. However, the amount of magnesium in the stool does not decrease appropriately (probably the secretion of magnesium is not greatly reduced), and the patient develops hypomagnesemia. Severe magnesium depletion is associated with steatorrheic syndromes.[76] Pathologic processes such as celiac disease, tropical and nontropical sprue, malignancies (characteristically lymphoma), surgical resection, intestinal bypass, and profound diarrhea have all been considered responsible for the development of hypomagnesemia. From 1960 to 1975, when the number of surgical bypass procedures for the treatment of obesity increased greatly, it was noted that many of these patients developed profound hypomagnesemia and tetany. Hypomagnesemia is especially prominent in patients with idiopathic steatorrhea and diseases affecting the terminal ileum.

As described before, the characterization of TRPM6 mutations demonstrated a key role in hypomagnesemia and hypocalcemia secondary to a decrease in intestinal absorption and renal reabsorption of magnesium.

Hypomagnesemia Secondary to Decreased Magnesium Intake

Magnesium depletion has been described in children with protein-calorie malnutrition.[105] The hypomagnesemia results from a combination of decreased intake and GI losses due to diarrhea or severe vomiting. In a hospital setting, perhaps the most common cause of hypomagnesemia is prolonged therapy with intravenous fluids lacking magnesium. Often, when surgical patients require intestinal suction, they are given intravenous fluid, sometimes for several weeks, and seldom is magnesium added to the intravenous fluids. Alcoholism is probably the most common cause of hypomagnesemia in the United States.[191,306,447] The chronic ingestion of alcohol produces hypomagnesemia. The mechanisms are multifactorial. Usually patients with chronic alcoholism ingest diets poor in magnesium. Alcohol increases the urinary excretion of magnesium.[310] From the point of view of differential diagnosis, the clinical history, evidence of malnutrition, the presence of diarrhea and vomiting, or a history of surgery may help to differentiate individuals with decreased absorption of magnesium due either to a primary GI disease or to decreased intake from individuals with increased urinary excretion of magnesium. As mentioned previously, when there is decreased intake or absorption of magnesium from the GI tract, the amount of magnesium excreted in the urine is greatly reduced, on the order of 10 to 15 mg per day.

Hypomagnesemia Secondary to Increased Urinary Losses of Magnesium

Because 60% to 70% of magnesium is absorbed in the TAL of the loop of Henle, any factor that blocks the reabsorption of sodium chloride in this part of the nephron will also promote the urinary excretion of magnesium. In conditions in which the ECF volume is increased and in entities characterized by profound diuresis (diuretic phase of acute tubular necrosis, postobstructive diuresis), the patient may excrete 20% to 30% of the filtered load of magnesium and may develop profound hypomagnesemia. Administration of large amounts of diuretics such as ethacrynic acid, bumetanide, or furosemide has a significant effect on renal magnesium excretion. Patients with ketoacidosis may develop hypomagnesemia. Serum magnesium, phosphorus, and potassium concentrations may be elevated during periods of ketoacidosis; however, the levels usually fall after the administration of insulin and fluid replacement. Increased excretion of magnesium has been seen after the treatment of diabetic ketoacidosis[104] and in metabolic conditions characterized by an excess of mineralocorticoids[276] such as primary aldosteronism. A specific defect has been described in patients receiving aminoglycosides[318] or cisplatin (an antitumoral agent).[580] The usual lesions produced by aminoglycosides are acute tubular necrosis, renal insufficiency, and hypermagnesemia; however, several patients have developed a specific tubular defect characterized by profound hypermagnesuria and hypomagnesemia that may persist for several weeks after the drug is discontinued. Some of these patients also developed hypokalemia.

Gitelman Syndrome

Patients with chronic hypokalemia and a phenotype other than that of Bartter syndrome, who have hypomagnesemia and excess urinary magnesium, are described as having Gitelman syndrome.[223] Gitelman syndrome is actually more common than Bartter syndrome and is characterized as follows. The patients may be children or adults with primary renal tubular hypokalemic metabolic alkalosis with magnesium deficiency, hypocalciuria, and skin lesions. Hyperreninemic hyperaldosteronism is present, as are the other features of Bartter syndrome. The inheritance is autosomal recessive, and linkage analysis to the locus encoding the renal thiazide–sensitive Na-Cl cotransporter is uniform.[614] Thus, reduced sodium chloride reabsorption in the diluting segment is the pathogenesis of the disease, and it further leads to abnormalities in magnesium transport.

Treatment of Alterations in Magnesium Metabolism

Hypermagnesemia

Hypermagnesemia is seen very seldom in clinical medicine. In general, it is observed in patients with far-advanced renal insufficiency, usually with a GFR of less than 10 mL per minute. The treatment is similar to that for hypercalcemia (i.e., volume expansion with saline and administration of furosemide). However, care is required because this therapeutic regimen will also increase the excretion of calcium in the urine and potentiate the toxic effects of hypermagnesemia. Thus, if expansion with saline and furosemide is used, calcium should be added to the solutions, approximately 1 to 3 ampules of calcium gluconate per liter of saline, to prevent hypocalcemia. If the patient's GFR is extremely low, and volume expansion with saline and diuretics is not effective, dialysis with a low or zero magnesium dialysate should be instituted. Hypermagnesemia is also seen clinically when large amounts of magnesium are given intravenously to patients. A decrease in the dose administered will rapidly correct the condition.

Hypomagnesemia

Profound magnesium depletion may be accompanied by hypocalcemia and tetany. Thus, the treatment of severe hypomagnesemia may constitute a medical emergency. Profound hypomagnesemia can be easily corrected by administration of magnesium intravenously, provided that the patient has fairly normal renal function. In patients with compromised renal function, magnesium should be given cautiously, and serum magnesium should be closely monitored. Fifty to 75 mEq of magnesium sulfate or magnesium chloride should be mixed in 500 mL of dextrose in water and given intravenously over 6 to 8 hours. The next morning, serum magnesium should be measured and, if hypomagnesemia persists, the amount of magnesium should be increased to 100 mEq dissolved in the same type of solution and given over 8 hours. In some circumstances, this procedure should be repeated two or three times until the serum magnesium level increases to 2.5 mg per dL. If the patient requires magnesium orally over a prolonged period, magnesium salts can be given to these patients. One gram of magnesium oxide has roughly 50 mEq, or 600 mg, of magnesium. Thus, magnesium oxide in a dose of 250 to 500 mg can be given to patients two to four times daily. Larger doses are not well tolerated, and most patients will develop diarrhea. It is important to emphasize that a normal diet provides approximately 25 mEq, or 300 mg, of magnesium.

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REFERENCES

1. The Physiological and Cellular Basis of Metabolic Bone Disease. Baltimore: Williams & Wilkins Co.; 1974.
2. Bone Histomorphometry. New York: Raven Press; 1994.
3. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. The HYP Consortium. Nat Genet. 1995;11:130. http://www.ncbi.nlm.nih.gov/pubmed/7550339
4. Autosomal dominant hypophosphatasemic rickets is associated with mutations in FGF23. Nat Genet. 2000;26:345. http://www.ncbi.nlm.nih.gov/pubmed/11062477
5. Aasebø W Scott H, Ganss R. Kidney biopsies taken before and after oral sodium phosphate bowel cleansing. Nephrol Dial Transplant. 2007;22:920. http://www.ncbi.nlm.nih.gov/pubmed/17138571
6. Abassi AA, Chemplavil JK, Farah S. Hypercalcemia in active tuberculosis. Ann Intern Med. 1979;90:324. http://www.ncbi.nlm.nih.gov/pubmed/426400
7. Adams JS, Sharma OP, Singer FR. Metabolism of 25-hyperoxyvitamin D3 by alveolar macrophages in sarcoidosis. Clin Res. 1983;31:499A. http://www.ncbi.nlm.nih.gov/pubmed/6688814
8. Aderka D, Shoenfeld Y, Santo M, et al. Life-threatening hypophosphatemia in a patient with acute myelogenous leukemia. Acta Haematol. 1980;64:117. http://www.ncbi.nlm.nih.gov/pubmed/6776768
9. Agus ZS, Gardner LB, Beck LH, et al. Effects of parathyroid hormone on renal tubular reabsorption of calcium, sodium and phosphate. Am J Physiol. 1973;224:1143.
10. Agus ZS, Goldfarb S, Wasserstein A. eds. Disorders of Calcium and Phosphate Balance. In: Brenner BM, Rector FCJ, eds. The Kidney. Philadelphia: Saunders, 1981; 940.
11. Ahmed KY, Varghese Z, Willis MR, et al. Persistent hypophosphatemia and osteomalacia in dialysis patients not on oral phosphate-binders: Response to dihydrotachysterol therapy. Lancet. 1976;1:439. http://www.ncbi.nlm.nih.gov/pubmed/55715
12. Aikawa JK, Rhoades EL, Gordon GS. Urinary and fecal excretion of orally administered Mg^{2+}. Proc Soc Exp Biol Med. 1958;98:29. http://www.ncbi.nlm.nih.gov/pubmed/13554531
13. Albright F, Burnett CH, Smith PH, Parson W Pseudohypoparathyroidism—an example of "Seabright-Bantam syndrome". Endocrinology. 1942;30:922.
14. Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty in females. N Eng J Med. 1937;216:727.
15. Albright F, Forbes AP, Hinneman PH. Pseudopseudohypoparathyroidism. Trans Assoc Am Physicians. 1952;65:337. http://www.ncbi.nlm.nih.gov/pubmed/13005676
16. Alcalde AI, Sarasa M, Raldua D, et al. Role of thyroid hormone in regulation of renal phosphate transport in young and aged rats. Endocrinology. 1999;140:1544. http://www.ncbi.nlm.nih.gov/pubmed/10098486
17. Alfrey AC, Miller NL. Bone magnesium pools in uremia. J Clin Invest. 1973;52:3019.
18. Ambuhl PM, Zajicek HK, Wang H, et al. Regulation of renal phosphate transport by acute and chronic metabolic acidosis in the rat. Kidney Int. 1998;53:1288.
19. Amling M, Priemel M, Holzmann T, et al. Rescue of the skeletal phenotype of vitamin D receptor-ablated mice in the setting of normal mineral ion homeostasis: Formal histomorphometric and biomechanical analyses. Endocrinology. 1999;140:4982.
20. Anast CA, Winnocker JL, Forte LR. Impaired release of parathyroid hormone in magnesium deficiency. J Clin Endocrinol. Metab. 1976;42:707. http://www.ncbi.nlm.nih.gov/pubmed/177448
21. Anast CW, Mohs JM, Kaplan SL. Evidence for parathyroid failure in magnesium deficiency. Science. 1972;177:606. http://www.ncbi.nlm.nih.gov/pubmed/5049304
22. Arar M, Baum M, Biber J, Murer H, Levi M. Epidermal growth factor inhibits Na-Pi cotransport and mRNA in OK cells. Am J Physiol. 1995;268:309. http://www.ncbi.nlm.nih.gov/pubmed/7864171
23. Arar M, Zajicek HK, Elshihabi I, Levi M. Epidermal growth factor inhibits Na-Pi cotransport in weaned and suckling rats. Am J Physiol. 1999;276:72.
24. Argiro L, Desbarats M, Glorieux FH, Ecarot B. Mepe, the gene encoding a tumor-secreted protein in oncogenic hypophosphatemic osteomalacia, is expressed in bone. Genomics. 2001;74:342. http://www.ncbi.nlm.nih.gov/pubmed/11414762
25. Arieff AI, Massry SG. Calcium metabolism of brain in acute renal failure. J Clin Invest. 1974;53:387. http://www.ncbi.nlm.nih.gov/pubmed/11344551

26. Arima K, Hines ER, Kiela PR, Drees JB, Collins JF, Ghishan FK. Glucocorticoid regulation and glycosylation of mouse intestinal type IIb Na-P(i) cotransporter during ontogeny. Am J Physiol. Gastrointest Liver Physiol. 2002;283:426.
http://www.ncbi.nlm.nih.gov/pubmed/12121891

27. Arnaud CD, Clar OH. eds. Primary Hyperparathyroidism. In: Krieger DT, Bardin CW, eds. Current Therapy in Endocrinology 1983–1984. Philadelphia and St. Louis: Decker and Mosby, 1983; 270.

28. Arnold A, Brown MF, Urena P, Gaz RD, Sarfati E, Drueke TB. Monoclonality of parathyroid tumors in chronic renal failure and in primary parathyroid hyperplasia. J Clin Invest. 1995;95:2047.

29. Atkins D, Ibbotson KJ, Hillier K. Secretion of prostaglandins as bone resorbing agents by renal cortical carcinoma in culture. Br J Cancer. 1971;36:601.
http://www.ncbi.nlm.nih.gov/pubmed/201261

30. Ba J, Friedman PA. Calcium-sensing receptor regulation of renal mineral ion transport. Cell Calcium. 2004;35:229.
http://www.ncbi.nlm.nih.gov/pubmed/15200146

31. Bachmann S, Schlichting U, Geist B, et al. Kidney-specific inactivation of the megalin gene impairs trafficking of renal inorganic sodium phosphate cotransporter (NaPi-IIa). J Am Soc Nephrol. 2004;15:892.
http://www.ncbi.nlm.nih.gov/pubmed/15034091

32. Bacic D, Schulz N, Biber J, et al. Involvement of the MAPK-kinase pathway in the PTH-mediated regulation of the proximal tubule type IIa Na+/Pi cotransporter in mouse kidney 88. Pfugers Arch. 2003;446:52.
http://www.ncbi.nlm.nih.gov/pubmed/12690463

33. Bacic D, Wagner CA, Hernando N, Kaissling B, Biber J, Murer H. Novel aspects in regulated expression of the renal type IIa Na/Pi-cotransporter. Kidney Int. Suppl 2004;66:S5–S12.

34. Bacskai BJ, Friedman PA. Activation of latent Ca^{2+} channels in renal epithelial cells by parathyroid hormone. Nature. 1990;347:388.
http://www.ncbi.nlm.nih.gov/pubmed/1699128

35. Bai X, Miao D, Li J, Goltzman D, Karaplis AC. Transgenic mice overexpressing human fibroblast growth factor 23 (R176Q) delineate a putative role for parathyroid hormone in renal phosphate wasting disorders. Endocrinology. 2004; 145:5269.
http://www.ncbi.nlm.nih.gov/pubmed/15284207

36. Bai XY, Miao D, Goltzman D, Karaplis AC. The autosomal dominant hypophosphatemic rickets R176Q mutation in fibroblast growth factor 23 resists proteolytic cleavage and enhances in vivo biological potency. J Biol Chem. 2003;278:9843.
http://www.ncbi.nlm.nih.gov/pubmed/12519781

37. Baker LRI, Ackrill P, Cattell WR, Stamp TC, Watson L. Latrogenic osteomalacia and myopathy due to phosphate depletion. Br Med J. 1974;3:150.
http://www.ncbi.nlm.nih.gov/pubmed/4843652

38. Barbour GL, Coburn JW, Slatopolsky E. Hypercalcemia in an anephric patient with sarcoidosis: Evidence for extra-renal generation of 1,25-dihydroxyvitamin D. N Engl J Med. 1982;305:440.
http://www.ncbi.nlm.nih.gov/pubmed/6894783

39. Beall DP, Scofield RH. Milk-alkali syndrome associated with calcium carbonate consumption. Medicine. 1995;74:89.
http://www.ncbi.nlm.nih.gov/pubmed/7891547

40. Beck D, Levitin H, Epstein FH. The effect of intravenous infusion of calcium on renal concentrating ability. Am J Physiol. 1959;197:1118.

41. Beck LH, Goldberg M. Effects of acetazolamide and parathyroidectomy on renal transport of sodium, calcium and phosphate. Am J Physiol. 1973;224:1136.

42. Beck LH, Goldberg M. Mechanism of the blunted phosphaturia in saline-loaded thyroparathyroidectomized dogs. Kidney Int. 1974;6:18.
http://www.ncbi.nlm.nih.gov/pubmed/4417751

43. Beck N. Effect of metabolic acidosis on renal response to parathyroid hormone in phosphorus-deprived rats. Am J Physiol. 1981;241:F23–F27.

44. Beck N, Singh H, Reed SW. Pathogenic role of cyclic AMP in the impairment of urinary concentrating ability in acute hypercalcemia. J Clin Invest. 1974;54:1049.
http://www.ncbi.nlm.nih.gov/pubmed/4371361

45. Beers KW, Dousa TP. Thyroid hormone stimulates the Na(+)-PO4 symporter but not the Na(+)-SO4 symporter in renal brush border. Am J Physiol. 1993;265:323.

46. Bell HH, Stern PH, Pantzer E, Sinha TK, DeLuca HF. Evidence that increased circulating 1α,25-dihydroxyvitamin D is the probable cause for abnormal calcium metabolism in sarcoidosis. J Clin Invest. 1979;64:218.
http://www.ncbi.nlm.nih.gov/pubmed/312811

47. Benet-Pages A, Lorenz-Depiereux B, Zischka H, et al. FGF23 is processed by proprotein convertases but not by PHEX. Bone. 2004;35:455.
http://www.ncbi.nlm.nih.gov/pubmed/15268897

48. Benet-Pages A, Orlik P, Strom TM, et al. An FGF23 missense mutation causes familial tumoral calcinosis with hyperphosphatemia. Hum Mol Genet. 2005;14:385–390.
http://www.ncbi.nlm.nih.gov/pubmed/15590700

49. Berenson J, Hirschberg R. Safety and convenience of a 15-minute infusion of zoledronic acid. Oncologist. 2004;9:319.
http://www.ncbi.nlm.nih.gov/pubmed/15169987

50. Bergwitz C, Roslin NM, Tieder M, et al. SLC34A3 mutations in patients with hereditary hypophosphatemic rickets with hypercalciuria predict a key tole for the sodium-phosphate cotransporter NaPi-IIc in maintaining phosphate homeostasis. Am J Hum Genet.. 2006;78:179.
http://www.ncbi.nlm.nih.gov/pubmed/16358214

51. Berliner BC, Shenker IR, Weinstock MS. Hypercalcemia associated with hypertension due to prolonged immobilization (an unusual complication of extensive burns). Pediatrics. 1972;49:92.
http://www.ncbi.nlm.nih.gov/pubmed/5059316

52. Berlyne GM, Ben-Ari J, Pest D, Weinberger J, et al. Hyperaluminaemia from aluminum resins in renal failure. Lancet. 1970;2:494.
http://www.ncbi.nlm.nih.gov/pubmed/4194940

53. Berndt T, Craig TA, Bowe AE, et al. Secreted frizzled-related protein 4 is a potent tumor-derived phosphaturic agent. J Clin Invest. 2003;112:785.
http://www.ncbi.nlm.nih.gov/pubmed/12952927

54. Berson SA, Yalow RS. Parathyroid hormone in plasma in adenomatous hy-perparathyroidism, uremia and bronchogenic carcinoma. Science. 1966;154:907.
http://www.ncbi.nlm.nih.gov/pubmed/4975444

55. Betro MG, Pain RW. Hypophosphatemia and hyperphosphatemia in a hospital population. Br Med J. 1972;1:273.
http://www.ncbi.nlm.nih.gov/pubmed/5008477

56. Better OS. Tubular dysfunction following kidney transplantation. Nephron. 1980;25:209.
http://www.ncbi.nlm.nih.gov/pubmed/6991964

57. Beutner EH, Munson PL. Time course of urinary excretion of inorganic phosphate by rats after parathyroidectomy and after injection of parathyroid extract. Endocrinology. 1960;66:610.
http://www.ncbi.nlm.nih.gov/pubmed/13800268

58. Bianco P, Riminucci M, Majolagbe A, et al. Mutations of the GNAS1 gene, stromal cell dysfunction, and osteomalacic changes in non-McCune-Albright fibrous dysplasia of bone. J Bone Miner Res. 2000;15:120.
http://www.ncbi.nlm.nih.gov/pubmed/10646121

59. Bianco P, Robey PG, Wientroub S. eds. Fibrous dysplasia of bone. In: Glorieux FH, Pettifor J, Juppner H., eds. Pediatric Bone Biology and Disease. New York: Academic Press, 2003; 509.

60. Biber J, Gisler SM, Hernando N, et al. PDZ interactions and proximal tubular phosphate reabsorption. Am J Physiol. Renal Physiol. 2004;287:871.

61. Biber J, Murer H. Na-P_i cotransport in LLC-PK1 cells: fast adaptive response to P_i deprivation. Am J Physiol. 1985;249:C430–C434.

62. Bikle DD, Munson S. 1,25-dihydroxyvitamin D increases calmodulin binding to specific proteins in the chick duodenal brush border membrane. J Clin Invest. 1985;76:2312.

63. Bikle DD, Munson S, Chafouleas J. Calmodulin may mediate 1,25-dihydroxyvitamin D-stimulated calcium transport. FEBS Lett. 1984;174:30.
http://www.ncbi.nlm.nih.gov/pubmed/6547914

64. Bilder D, Schober M, Perrimon N. Integrated activity of PDZ protein complexes regulates epithelial polarity. Nat Cell Biol. 2003;5:53.
http://www.ncbi.nlm.nih.gov/pubmed/12510194

65. Bilezikian JP, Brandi ML, Rubin M, et al. Primary hyperparathyroidism: new concepts in clinical, densitometric and biochemical features. J Intern Med. 2005;257:6.
http://www.ncbi.nlm.nih.gov/pubmed/15606372

66. Bilezikian JP, Silverberg SJ. Asymptomatic primary hyperparathyroidism. N Engl J Med. 2004;350:1746.

67. Blaine J, Okamura K, Giral H, et al. PTH-induced internalization of apical membrane NaPi2a: role of actin and myosin VI. Am J Physiol. Cell Physiol. 2009;297:C1339–C1346.

68. Blasco T, Aramayona JJ, Alcalde AI, et al. Rat kidney MAP17 induces cotrans-port of Na-mannose and Na-glucose in Xenopus laevis oocytes. Am J Physiol. Renal Physiol. 2003;285:799.

69. Block GA, Hulbert-Shearon TE, Levin NW, et al. Association of serum phosphorus and calcium X phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998;31:607–617.
http://www.ncbi.nlm.nih.gov/pubmed/9531176

70. Blumsohn A. What have we learnt about the regulation of phosphate metabolism? Curr Opin Nephrol Hypertens. 2004;13:397.
http://www.ncbi.nlm.nih.gov/pubmed/15199289

71. Body JJ, Dumon JC. Treatment of tumor-induced hypercalcemia with the bisphosphonate pamidronate: dose-response relationship and influence of tumor type. Ann Oncol. 1994;5:359.
http://www.ncbi.nlm.nih.gov/pubmed/8075034

72. Boelens PA, Norwood W, Kjellstrand C, et al. Hypophosphatemia with muscle weakness due to antacids and hemodialysis. Am J Dis Child. 1970;120:350. http://www.ncbi.nlm.nih.gov/pubmed/4924167

73. Bomsztyk K, Wright FS. Effects of transepithelial fluid flux on transepithelial voltage and transport of calcium, sodium, chloride and potassium by renal proximal tubule. Kidney Int. 1982;21:269.

74. Bonjour J-P, Philippe J, Guelpa G, et al. Bone and renal components in hypercalcemia of malignancy and response to a single infusion of clodronate. Bone. 1998;9:123. http://www.ncbi.nlm.nih.gov/pubmed/2971382

75. Bonjour JP, Preston C, Fleisch H. Effect of 1,25 dihydroxyvitamin D_3 on renal handling of P_i in thyroparathyroidectomized rats. J Clin Invest. 1977;60:1419. http://www.ncbi.nlm.nih.gov/pubmed/915006

76. Booth CC, Babouris N, Hanna S. Incidence of hypomagnesemia in intestinal malabsorption. Med J. 1963;2:141.

77. Bordier P, Rasmussen H, Marie P. Vitamin D metabolites and bone mineralization in man. Clin Endocrinol Metab. 1978;46:284.

78. Borke JL, Caride A, Verma AK. Plasma membrane calcium pump and 28-kDa calcium protein in cells of rat kidney distal tubules. Am J Physiol. 1989;257:F842.

79. Borke JL, Minami J, Verma A, et.al. Monoclonal antibodies to human erythrocyte membrane Ca^{++} -Mg^{++} adenosine trisphosphatase pump recognize an epitope in the basolateral membrane of human kidney distal tubule cells. J Clin Invest. 1987;80:1225.

80. Bourdeau JE. Calcium transport across the cortical thick ascending limb of Henle's loop. In: Bronner F, Peterlik M, eds. Calcium and Phosphate Transport Across Biomembranes. New York: Academic Press; 1981:199. http://www.ncbi.nlm.nih.gov/pubmed/6250408

81. Bourdeau JE, Burg MB. Voltage dependence of calcium transort in the thick ascending limb of Henle's loop. Am J Physiol. 1979;236:F357.

82. Bourdeau JE, Burg MB. Effect of PTH on calcium transport across the thick ascending limb of Henle's loop. Am J Physiol. 1980;239:F121.

83. Bourdeau JE, Lau K. Basolateral cell membrane Ca-Na exchange in single rabbit connecting tubules. Am J Physiol. 1990;258:F1497–F1503.

84. Bowe AE, Finnegan R, Jan de Beur SM, et al. FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate. Biochem Biophys Res Commun. 2001;284:977. http://www.ncbi.nlm.nih.gov/pubmed/11409890

85. Boyce BF, Yoneda T, Lowe C, et al. Requirement of pp60c-src expression for osteoclasts to form ruffed borders and resorb bone in mice. J Clin Invest. 1992;90:1622.

86. Boyce TM, Bloebaum RD. Cortical aging differences and fracture implications for the human femoral neck. Bone. 1993;14:769. http://www.ncbi.nlm.nih.gov/pubmed/8268051

87. Brame LA, White KE, Econs MJ. Renal phosphate wasting disorders: clinical features and pathogenesis. Semin Nephrol. 2004;24:39. http://www.ncbi.nlm.nih.gov/pubmed/14730508

88. Braun J, Oldendorf M, Moshage W, et al. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. AJKD. 1996;27:394. http://www.ncbi.nlm.nih.gov/pubmed/8604709

89. Brereton HD, Halushka PV, Alexander RW. Indomethacin-responsive hypercalcemia in a patient with renal cell adenocarcinoma. N Engl J Med. 1974; 291:83. http://www.ncbi.nlm.nih.gov/pubmed/4835887

90. Bresler D, Bruder J, Mohnike K, et al. Serum MEPE-ASARM-peptides are elevated in X-linked rickets (HYP): implications for phosphaturia and rickets. J Endocrinol. 2004;183:1.

91. Bretscher A, Edwards K, Fehon RG. ERM proteins and merlin: integrators at the cell cortex. Nat Rev Mol Cell Biol. 2002;3:586. http://www.ncbi.nlm.nih.gov/pubmed/12154370

92. Breusegem SY, Takahashi H, Giral-Arnal H, et al. Differential regulation of the renal sodium-phosphate cotransporters NaPi-IIa, NaPi-IIc, and PiT-2 in dietary potassium deficiency. Am J Physiol. Renal Physiol. 2009;297:F350–F361.

93. Brickman AS, Massry SG, Coburn JW. Changes in serum and urinary calcilum during treatment of hydrochlorothiazide studies on mechanisms. J Clin Invest. 1972;51:945. http://www.ncbi.nlm.nih.gov/pubmed/4552338

94. Bringhurst FR, Demay MB, Kronenberg HM. eds. Hormones and disorders of mineral metabolism. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, eds. Williams Textbook of Endocrinology. Philadelphia: WB. Saunders; 2003:1303.

95. Bronner F, Siepchenko B, Wood RJ, et al. The role of passive transport in calcium absorption [letter]. J Nutr. 2003;133:1426.

96. Brown EM, Gamba G, Riccardi D, et al. Cloning and characterization of an extracellular Ca2+-sensing receptor from bovine parathyroid. Nature. 1993;366:575–580. http://www.ncbi.nlm.nih.gov/pubmed/8255296

97. Brown EM, Hebert SC. A cloned Ca^{2+}-sensing receptor; a mediator of direct effects of extracellular Ca^{2+} on renal function? J Am Soc Nephrol. 1995;6:1530.

98. Brunette MG, Vigneault N, Carriere S. Micropuncture study of magnesium transport along the nephron in the young rat. Am J Physiol. 1974;227:891. http://www.ncbi.nlm.nih.gov/pubmed/4429138

99. Brunette MG, Vigneault N, Carriere S. Micropouncture study of renal magnesium transport in magnesium-loaded rats. Am J Physiol. 1975;229:1695. http://www.ncbi.nlm.nih.gov/pubmed/1211503

100. Brunvand L, Haga P, Tangsrud SE, et al. Congestive heart failure caused by vitamin D deficiency? Acta Paediatr. 1995;84:106. http://www.ncbi.nlm.nih.gov/pubmed/7734890

101. Buckle RH, Care AD, Cooper CW. The influence of plasma magnesium concentration on parathyroid hormone secretion. J Endocrinol. 1968;42:529. http://www.ncbi.nlm.nih.gov/pubmed/5715979

102. Burgess TL, Qian Y-X, Kaufman S, Ring BD, et al. The ligand for osteoprotegrin (OPGL) directly activates mature osteoclasts. J Cell Biol. 1999;145:527. http://www.ncbi.nlm.nih.gov/pubmed/10225954

103. Busch AE, Schuster A, Waldegger S. Expression of a renal type I sodium/ phosphate transporter (NaPi-1) induces a conductance in Xenopus oocytes permeable for organic and inorganic anions. Proc Natl Acad Sci U S A. 1996;93:5347. http://www.ncbi.nlm.nih.gov/pubmed/8643577

104. Butler AM, Talbot NB, Burnett CH. Metabolic studies in diabetic coma. Trans Assoc Am Physicians. 1947;60:102. http://www.ncbi.nlm.nih.gov/pubmed/18917248

105. Caddell JL, Goddard DR. Studies in protein-calorie malnutrition 1. Chemical evidence for magnesium deficiency. N Engl J Med. 1967;275:533. http://www.ncbi.nlm.nih.gov/pubmed/6019762

106. Caldas YA, Giral H, Cortazar MA, et al. Liver X receptor-activating ligands modulate renal and intestinal sodium-phosphate transporters. Kidney Int. 2011;80:535. http://www.ncbi.nlm.nih.gov/pubmed/21677638

107. Cao TT, Deacon HW, Reczek D, et al. A kinase-regulated PDZ-domain interaction controls endocytic sorting of the beta2-adrenergic receptor. Nature. 1999;401:286. http://www.ncbi.nlm.nih.gov/pubmed/10499588

108. Capuano P, Bacic D, Stange G, et al. Expression and regulation of the renal Na/phosphate cotransporter NaPi-IIa in a mouse model deficient for the PDZ protein PDZK1. Pfuegers Arch. 2004;449:392.

109. Carafoli E. Calcium pump of the plasma membrane. Phys Rev. 1991;71:129. http://www.ncbi.nlm.nih.gov/pubmed/1986387

110. Carone FA. The effects upon the kidney of transient hypercalcemia induced by parathyroid extract. Am J Pathol. 1960;36:77. http://www.ncbi.nlm.nih.gov/pubmed/13807842

111. Caroni P, Reinlib L, Carafoli E. Charge movements during the Na^{+}-Ca^{++} exchange in heart sarcolemmal vesicles. Proc Natl Acad Sci U S A. 1980;77:6354. http://www.ncbi.nlm.nih.gov/pubmed/6935649

112. Carpenter TO, Insogna KL. eds. The hypocalcemic disorders: Differential diagnosis and therapeutic use of vitamin D. In: Feldman D, Glorieux FH, Pike JW, eds. Vitamin D. San Diego: Academic Press, 1997; 923.

113. Caverzasio J, Brown CD, Biber J, et al. Adaptation of phosphate transport in phosphate-deprived LLC-PK1 cells. Am J Physiol. 1985;248:F122–F127.

114. Caverzasio J, Montessuit C, Bonjour J-P. Stimulatory effect of insulin-like growth factor-1 on renal Pi transport and plasma 1,25-dihydroxyvitamin D_3. Endocrinol. 1990;127:453. http://www.ncbi.nlm.nih.gov/pubmed/2361480

115. Chabardes D, Imbert M, Clique A, Montegut M, Morel F. PTH sensitive adenyl cyclase activity in different segments of the rabbit nephron. Pfugers Arch (Euro J Physiol). 1975;354:229. http://www.ncbi.nlm.nih.gov/pubmed/163468

116. Chabardes D, Imbert-TeBoule M, Clique A. Distribution of calcitonin-sensitive adenylate cyclase along the rabbit kidney tubule. Proc Natl Acad Sci U S A. 1976;73:3608.

117. Chase LR, Melson GL, Aurbach GD. Pseudohypoparathyroidism: Defective excretion of 3′-5′-AMP in response to parathyroid hormone. J Clin Invest. 1969;48:1832.

118. Chase LR, Slatopolsky E. Secretion and metabolic efficacy of parathyroid hor-mone in patients with severe hypomagnesemia. J Clin Endocrinol Metab. 1974;38:363.

119. Chen TL, Hirst MA, Cone CM, Hochberg Z, Tietze H-U, Feldman D. 1,25-dihydroxyvitamin D resistance, rickets and alopecia: Analysis of receptors and bioresponse in cultured fibroblasts from patients and parents. J Clin Endocrinol Metab. 1984;59:383.

120. Chertow GM. Slowing the progression of vascular calcification in hemodialysis. J Am Soc Neph. 2003;14:S310–S314.

121. Chertow GM, Burke SK, Lazarus JM, et al. Poly[allylamine hydrochloride] (RenaGel): a noncalcemic phosphate binder for the tratment of hyperphosphatemia in chronic renal failure. AJKD. 1997;29:66.
http://www.ncbi.nlm.nih.gov/pubmed/9002531
122. Chertow GM, Burke SK, Dillon MA, et al. Long-term effects of sevelamer hydrochloride on the calcium × phosphate product and lipid profile of haemodialysis patients. Nephrol Dial Transplant.1999;14:2907.
http://www.ncbi.nlm.nih.gov/pubmed/10570096
123. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int. 2002;62:245.
http://www.ncbi.nlm.nih.gov/pubmed/12081584
124. Chesney PJ, Davis JP, Purdy WK, Wand PJ, Chesney RW. Clinical manifestations of toxic shock syndrome. JAMA. 1981;246:741.
http://www.ncbi.nlm.nih.gov/pubmed/7253137
125. Chiemchaisri H, Phillips PH. Certain factors including fuoride which affect magnesium calcinosis in the dog and rat. J Nutrition. 1965;86:23.
http://www.ncbi.nlm.nih.gov/pubmed/14291680
126. Chopra D, Janson P, Sawin CT. Insensitivity to digoxin associated with hypocalcemia. N Engl J Med. 1977;296:917.
http://www.ncbi.nlm.nih.gov/pubmed/846513
127. Chou YH, Pollak MR, Brandi ML, et al. Mutations in the human Ca2+ -sensing-receptor gene that cause familial hypocalciuric hypercalcemia. Am J Hum Genet. 1995;56:1075.
128. Coburn J, Slatopolsky E. eds. Vitamin D, PTH and renal osteodystrophy. In: Brenner B, Rector F, eds. The Kidney. Philadelphia: Saunders, 1981; 2213.
129. Coburn JW, Brautbar N. eds. Disease states and related to Vitamin D. In: Norman AW, Decker M, eds. Vitamin D, Clinical and nutritional aspects. New York: 1986.
130. Coburn JW, Massry SG. Changes in serum and urinary calcium during phosphate depletion: Studies on mechanisms. J Clin Invest. 1970;49:1073.
http://www.ncbi.nlm.nih.gov/pubmed/5422013
131. Coburn JW, Massry SG, DePalma JR. Rapid appearance of hypercalcemia with initiation of hemodialysis. J Am Med Assoc. 1969;210:2276.
http://www.ncbi.nlm.nih.gov/pubmed/5395424
132. Cohen EP, Trivedi C. Hypercalcemia from non-prescription vitamin A. Nephrol Dial Transplant. 2004;19:2929.
133. Cohen LF, Balow JE, Magrath IT, et al. Acute tumor lysis syndrome. A review of 37 patients with Burkitt's lymphoma. Am J Med. 1980;68:486.
http://www.ncbi.nlm.nih.gov/pubmed/7369230
134. Collins MT, Chebli C, Jones J, et al. Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia, J Bone Miner Res. 2001;16:806.
135. Connor TB, Rosen BL, Blaustein MP. Hypocalcemia precipitating congestive heart failure. N Engl J Med. 1982;307:869.
http://www.ncbi.nlm.nih.gov/pubmed/7110262
136. Connor TBP, Toskes J, Mahaffey LG. Parathyroid functon during chronic magnesium deficiency. Johns Hopkins Med J. 1972;131:100.
http://www.ncbi.nlm.nih.gov/pubmed/5050732
137. Connors MH, Irias JJ, Golabi M. Hypo-hyperparathyroidism: evidence for a defective parathyroid hormone. Pediatrics. 1977;60:343.
http://www.ncbi.nlm.nih.gov/pubmed/197477
138. Constanzo LS. Localization of diuretic action in microperfused rat distal tubules; Ca and Na transport. Nature. 1990;347:388.
139. Cooke N, Teitelbaum S, Avioli LV. Antacid-induced osteomalacia and nephrolithiasis. Arch Intern Med. 1978;138:1007.
http://www.ncbi.nlm.nih.gov/pubmed/646554
140. Corsi A, Collins MT, Riminucci M, et al. Osteomalacic and hyperparathyroid changes in fibrous dysplasia of bone: core biopsy studies and clinical correlations. J Bone Miner Res. 2003;18:1235.
http://www.ncbi.nlm.nih.gov/pubmed/12854833
141. Coulter-Mackie MB, Tung A, Henderson HE, et al. The AGT gene in Africa: a distinctive minor allele haplotype, a polymorphism (V326I), and a novel PH1 mutation (A112D) in black Africans. Mol Genet Metab. 2003;78:44.
http://www.ncbi.nlm.nih.gov/pubmed/12559847
142. Craddock PR, Yawata Y, Van Santen L, et ak. Acquired phagocyte dysfunction: A complication of the hypophosphatemia of parental hyperalimentation. N Engl J Med. 1974;290:1403.
http://www.ncbi.nlm.nih.gov/pubmed/4208370
143. Crook M, Swaminathan R, Schey S. Hypophosphataemia in patients undergoing bone marrow transplantation. Leuk Lymphoma. 1996;22:335.
http://www.ncbi.nlm.nih.gov/pubmed/8819083
144. Cuche JL, Ott CE, Marchand GR, Diaz-Buxo JA, Knox FG. Intrarenal calcium in phosphate handling. Am J Physiol. 1976;230:790.
http://www.ncbi.nlm.nih.gov/pubmed/1266984
145. Cummings KB, Robertson RP. Prostaglandin: Increased production by renal cell carcinoma. J Urol. 1977;118:720.
http://www.ncbi.nlm.nih.gov/pubmed/916087
146. Dachille RD, Goldberg JS, Wexler ID, Shons AR. Fibrous dysplasia-induced hypocalcemia/rickets. J Oral Maxillofac Surg. 1990;48:1319.
147. Davies MR, Lund RJ, Hruska KA. BMP-7 is an efficacious treatment of vascular calcification in a murine model of atherosclerosis and chronic renal failure. J Am Soc Nephrol. 2003;14:1559.
148. Davies MR, Lund RJ, Mathew S, et al. Low turnover osteodystrophy and vas-cular calcification are amenable to skeletal anabolism in an animal model of chronic kidney disease and the metabolic syndrome. J Am Soc Nephrol. 2005;16:917–928.
http://www.ncbi.nlm.nih.gov/pubmed/15743994
149. Davis RH, Fourman P, Smith JWG. Prevalence of parathyroid insufficiency after thyroidectomy. Lancet. 1961;2:1432.
http://www.ncbi.nlm.nih.gov/pubmed/13883961
150. De Beur SM, Finnegan RB, Vassiliadis J, et al. Tumors associated with oncogenic osteomalacia express genes important in bone and mineral metabolism. J Bone Miner Res. 2002;17:1102.
http://www.ncbi.nlm.nih.gov/pubmed/12054166
151. De Niu P, Olsen HS, Gentz R, et al. Immunolocalization of stanniocalcin in human kidney. Mol Cell Endocrinol. 1998;137:155.
http://www.ncbi.nlm.nih.gov/pubmed/9605517
152. de Sanctis L, Vai S, Andreo MR, et al. Brachydactyly in 14 genetically characterized pseudohypoparathyroidism type Ia patients. J Clin Endocrinol. Metab. 2004;1989:1650.
153. DeFronzo RA, Cooke CR, Andres R. The effect of insulin on renal handling of sodium, potassium, calcium and phosphate in man. J Clin Invest. 1975;55:845.
154. DeFronzo RA, Goldberg M, Agus ZS. The effects of glucose and insulin on renal electrolyte transport. J Clin Invest. 1976;58:83.
http://www.ncbi.nlm.nih.gov/pubmed/932211
155. DeFronzo RA, Lang R. Hypophosphatemia and glucose intolerance: evidence for tissue insensitivity to insulin. N Engl J Med. 1980;303:1259.
http://www.ncbi.nlm.nih.gov/pubmed/6999353
156. Denda M, Finch J, Slatopolsky E. Phosphorus accelerates the development of parathyroid hyperplasia and secondary hyperparathyroidism in rats with renal failure. AJKD. 1996;28:596.
http://www.ncbi.nlm.nih.gov/pubmed/8840952
157. Deol H, Stasko SE, De Niu P, et al. Post-natal ontogeny of stanniocalcin gene expression in rodent kidney and regulation by dietary calcium and phosphate. Kidney Int. 2001;60:2142.
http://www.ncbi.nlm.nih.gov/pubmed/11737588
158. DeRouffignac C, DiStefano A, Wittner M, et al. Consequences of different effects of ADH and other peptide hormones on thick ascending limb of mammalian kidney. Am J Physiol. 1991;260:R1023.
159. DeRouffignac C, Mandon B, Wittner M, et al. Hormonal control of renal magnesium handling. Min Elec Metab. 1993;19:226.
http://www.ncbi.nlm.nih.gov/pubmed/8264508
160. DeRouffignac C, Quamme G. Renal magnesium handling and its hormonal control. Phys Rev. 1994;74:305.
161. DiGeorge AM. Congenital absence of the thymus and its immunologic con-sequence: Concurrence with congenital hypoparathyroidism. Birth Defects. 1968;4:16.
162. DiStefano A, Wittner M, Nitschke R, et al. Effects of glucagon on Na^+, Cl^-,K^+, Mg^{2+}, and Ca^{2+} transports in cortical medullary thick ascending limbs of mouse kidney. Pfugers Arch. 1989;414:640.
http://www.ncbi.nlm.nih.gov/pubmed/2813041
163. Ditzel J. Changes in red cell oxygen release capacity in diabetes mellitus. Fed Proc. 1979;38:2484.
http://www.ncbi.nlm.nih.gov/pubmed/39792
164. Ditzler JW. Epsom salts poisoning and a review of magnesium-ion physiology. Anesthesiology. 1970;32:378.
http://www.ncbi.nlm.nih.gov/pubmed/5437871
165. Dominguez JH, Gray RW, Lemann JJ. Dietary phosphate deprivation in women and men: Effects on mineral and acid balances, parathyroid hormone and the metabolism of 25-OH-vitamin D. J Clin Endocrinol Metab. 1976;43:1056.
http://www.ncbi.nlm.nih.gov/pubmed/11224
166. Dominguez JH, Juhaszova M, Feister HA. The renal sodium-calcium exchanger. J Lab Clin Med.. 1992;119:640.
http://www.ncbi.nlm.nih.gov/pubmed/1593210
167. Dominguez JH, Mann C, Rothrock JK, et al. Na^+ -Ca^{2+} exchange and Ca^{2+} depletion in proximal tubules. Am J Physiol. 1991;261:F328.
168. Dong Z, Saikumar P, Griess GA, et al. Intracellular Ca2+ thresholds that determine survival or death of energy-deprived cells. Am J Pathol. 1998;152;231.

169. Drezner M, Neelon FA, Lebovitz HE. Pseudohypoparathyroidism type II: A possible defect in the reception of the cyclic AMP signal. N Engl J Med. 1973;289:1056.
http://www.ncbi.nlm.nih.gov/pubmed/4355058
170. Driman DK, Kobrin MS, Kudlow JE, et al. Transforming growth factor-alpha in normal and neoplastic human endocrinal tissues. Hum Pathol. 1992;23:1360.
171. Duarte CG, Watson JG. Calcium reabsorption in proximal tubule of the dog nephron. Am J Physiol. 1967;212:1355.
http://www.ncbi.nlm.nih.gov/pubmed/4952126
172. Ducy P, Zhang R, Geoffroy V, et al. Osf2/Cbfa1: A transcriptional activator of osteoblast differentiation. Cell 1997;89:747.
173. Dudley HR, Ritchie AC, Schilling A. Pathological changes associated with the use of sodium ethylene diamine tetra-acetate in the treatment of hypercalcemia. N Engl J Med. 1955;252:331.
http://www.ncbi.nlm.nih.gov/pubmed/13236025
174. Dunlay R, Hruska KA. Parathyroid hormone receptor coupling to phospholipase C is an alternate pathway of signal transduction in the bone and kidney. Am J Physiol. 1990;258:F223–F231.
175. Dunn MJ. Magnesium depeletion in the rhesus monkey: Induction of magnesium-dependent hypocalcaemia. Clin Sci Mol Med. 1971;41:333.
http://www.ncbi.nlm.nih.gov/pubmed/5097476
176. Dusso AS, Lu Y, Pavlopoulos T, et al. A role of enhanced expression of transforming growth factor alpha (TGF-alpha) in the mitogenic effect of high dietary phosphorus on parathyroid cell growth in uremia. J Am Soc Neph. 1999;10;617.
177. Dyckner T, Webster PO. Ventricular extrasystoles and intracellular electrolytes before and after potassium and magnesium infusions in patients on diuretic therapy. Am Heart J. 1979;97:12.
http://www.ncbi.nlm.nih.gov/pubmed/83101
178. Eberle M, Traynor-Kaplan AE, Sklar LA, et al. Is there a relationship between phosphatidylinositol trisphosphate and F-actin polymerization in human neutrophils? J Biol Chem. 1990;265:16725.
http://www.ncbi.nlm.nih.gov/pubmed/2211588
179. Edwards BR, Baer PG, Sutton RA, et al. Micropuncture study of diuretic effects on sodium and calcium reabsorption in the dog nephron. J Clin Invest. 1973;52:2418.
180. Elalouf JM, Roinel N, DeRouffignac C. ADH-like effects of calcitonin on electrolyte transport by Henle's loop of rat kidney. Am J Physiol. 1984;246: F213–F220.
181. Emmett M, Goldfarb S, Agus ZS, et al. The pathophysiology of acid-base changes in chronically phosphate-depleted rats: bone-kidney interactions. J Clin Invest. 1977;59:291.
http://www.ncbi.nlm.nih.gov/pubmed/833276
182. Euzet S, Lelievre-Pegorier M, Merlet-Benichou C. Maturation of rat renal phosphate transport: effect of triiodothyronine. J Physiol. 1995;488 (Pt 2):449.
http://www.ncbi.nlm.nih.gov/pubmed/8568683
183. Euzet S, Lelievre-Pegorier M, Merlet-Benichou C. Effect of 3,5,3′-triiodothyronine on maturation of rat renal phosphate transport: kinetic characteristics and phosphate transporter messenger ribonucleic acid and protein abundance. Endocrinology. 1996;137:3522.
http://www.ncbi.nlm.nih.gov/pubmed/8754782
184. Evers C, Murer H, Kinne R. Effect of parathyrin on the transport properties of isolated renal brush-border vesicles. Biochem J. 1978;172:49.
http://www.ncbi.nlm.nih.gov/pubmed/207266
185. Falls WFJ, Stacey WK. Postobstructive diuresis. Studies in a dialyzed patient with a solitary kidney. Am J Med. 1973;54:404.
http://www.ncbi.nlm.nih.gov/pubmed/4689235
186. Farrington K, Varghese Z, Newman SP, et al. Dissociation of absorptions of calcium and phosphate after successful cadaveric renal transplantation. Br Med J. 1979;1:712.
http://www.ncbi.nlm.nih.gov/pubmed/373843
187. Feldman D, Chen T, Cone C, et al. Vitamin D resistant rickets with alopecia: cultured skin fibroblasts exhibit defective cytoplasmic receptors and unresponsiveness to $1,25(OH)_2D_3$. J Clin Endocrinol Metab. 1982;55:1020.
188. Feng JQ, Ward LM, Liu S, et al. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. Nat Genet. 2006;38:1310.
http://www.ncbi.nlm.nih.gov/pubmed/17033621
189. Filipovic D, Sackin H. A calcium-permeable stretch-activated cation channel in renal proximal tubule. Am J Physiol. 1991;260:F119.
190. Fleet JC, Wood RJ. Specific $1,25(OH)_2D_3$-mediated regulation of transcellular calcium transport in Caco-2 cells. Am Physiol Soc. 1999;276:G958–G964.
191. Flilnk EB, Stutzman FL, Anderson AR. Magnesium deficiency after prolonged parenteral f uid administration and after chronic alcoholism, complicated by delirium tremens. J Lab Clin Med. 1954;43:169.
http://www.ncbi.nlm.nih.gov/pubmed/13130933
192. Foley RN. Phosphorus comes of age as a cardiovascular risk factor. Arch Intern Med. 2007;167:873.
http://www.ncbi.nlm.nih.gov/pubmed/17502525
193. Folpe AL, Fanburg-Smith JC, Billings SD, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. Am J Surg Pathol. 2004;28:1.
http://www.ncbi.nlm.nih.gov/pubmed/14707860
194. Freitag J, Martin K, Conrades M. Evidence for skeletal resistance to parathyroid hormone magnesium depletion. J Clin Invest. 1979;64:1238.
http://www.ncbi.nlm.nih.gov/pubmed/227929
195. Frick A, Durasin I. Proximal tubular reabsorption of inorganic phosphate in adrenalectomized rats. Pf ugers Arch (Euro J Physiol). 1980;385:189.
http://www.ncbi.nlm.nih.gov/pubmed/7190681
196. Friedman NE, Lobaugh B, Drezner MK. Effects of calcitriol and phosphorus therapy on the growth of patients with X-linked hypophosphatemia. J Clin Endocrinol Metab. 1993;76:839.
http://www.ncbi.nlm.nih.gov/pubmed/8473393
197. Friedman PA. Mechanisms of renal calcium transport. Exp Nephrol. 2000; 8:343.
198. Friedman PA, Andreoli TE. CO2-stimulated NaCl absorption in the mouse renal cortical thick ascending limb of Henle. Evidence for synchronous Na+/H+ and Cl/HCO3-exchange in apical plasma membranes. J Gen Physiol. 1982;80:683.
http://www.ncbi.nlm.nih.gov/pubmed/6816900
199. Friedman PA, Figueiredo JF, Maack T, et al. Sodium-calcium interactions in renal proximal convoluted tubule of the rabbit. Am J Physiol. 1981;240:F558.
200. Friedman PA, Gesek FA. Calcium transport in renal epithelial cells. Am J Physiol. 1993;264:F181.
201. Friedman PA, Gesek FA. Cellular calcium transport in renal epithelia: measurement, mechanisms, and regulation. Physiol Rev 1995;75:429.
http://www.ncbi.nlm.nih.gov/pubmed/7624390
202. Fu GK, Lin D, Zhang MY, et al. Cloning of human 25-hydroxyvitamin D-1 alpha-hydroxylase and mutations causing vitamin D-dependent rickets type 1. Mol Endocrinol. 1997;11:1961.
http://www.ncbi.nlm.nih.gov/pubmed/9415400
203. Fucentese M, Murer H, Biber J. Expression of rat renal Na/cotransport of phosphate and sulfate in Sf9 insect cells. J Am Soc Nephrol. 1994;5:860.
204. Fuchs R, Peterlik M. eds. Intestinal phosphate transport. In: Massry SG, Ritz E, Jahn H, eds. Phosphate and Minerals in Health and Disease. New York: Plenum Press; 1980:381.
205. Fuller TJ, Nichols WW, Brenner BJ, et al. Reversible depression in myocardial performance in dogs with experimental phosphorus deficiency. J Clin Invest. 1978;62:1194.
206. Fulop M, Brazeau P. The phosphaturic effect of sodium bicarbonate and acetazolamide in dogs. J Clin Invest. 1968;47:983.
http://www.ncbi.nlm.nih.gov/pubmed/5645865
207. Furuse M, Fujita K, Hiiragi T, et al. Claudin-1 and -2: Novel integral membrane proteins localizing at tight junctions with no sequence similarity to occluding. J Cell Biol. 1998;141:1539.
208. Garabedian M, Silve C, Levy D, et al. Chronic hypophosphatemia in kidney transplanted children and young adults. Adv Exp Med Biol. 1980;128:249.
http://www.ncbi.nlm.nih.gov/pubmed/6999855
209. Gattineni J, Bates C, Twombley K, et al. FGF23 decreases renal NaPi-2a and NaPi-2c expression and induces hypophosphatemia in vivo predominantly via FGF receptor 1. Am J Physiol Renal Physiol. 2009;297:F282–F291.
210. Gazit D, Tieder M, Liberman UA, et al. Osteomalacia in hereditary hypophosphatemic rickets with hypercalciuria: a correlative clinical-histomor-phometric study. J Clin Endocrin Metab. 1991;72:229.
211. Gekle DJ, Stroder J, Rostock D. The effect of vitamin D on renal inorganic phosphate reabsorption on normal rats, parathyroidectomized rats, and rats with rickets. Pediatr Res. 1971;5:40.
212. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic apoL1 variants with kidney disease in African Americans. Science. 2010;329:841.
http://www.ncbi.nlm.nih.gov/pubmed/20647424
213. Gesek FA, Friedman PA. Mechanism of calcium transport stimulated by chlorothiazide in mouse distal convoluted tubule cells. J Clin Invest. 1992;90:429.
http://www.ncbi.nlm.nih.gov/pubmed/1322939
214. Gesek FA, Friedman PA. On the mechanism of parathyroid hormone stimulation of calcium uptake by mouse distal convoluted tubule cells. J Clin Invest. 1992;90:749.
http://www.ncbi.nlm.nih.gov/pubmed/1522230
215. Gesek FA, Friedman PA. Calclitonin stimulates calcium transport in distal convoluted tubule cells. Am J Physiol. 1993;264:F744.
216. Ghent S, Judson MA, Rosansky SJ. Refractory hypotension associated with hypocalcemia and renal disease. Am J Kidney Dis. 1994;23:430.
http://www.ncbi.nlm.nih.gov/pubmed/8128946

217. Giebisch G, Berger L, Pitts RF. The extra-renal response to acute acid-base disturbances of respiratory origin. J Clin Invest. 1955;34:231.
http://www.ncbi.nlm.nih.gov/pubmed/13233345
218. Gill JR, Bartter FC. On the impairment of renal concentrating ability in prolonged hypercalcemia and hypercalciuria in man. J Clin Invest. 1961;49:16.
219. Giral H, Lanzano L, Caldas Y, et al. Role of PDZK1 protein in apical membrane expression of renal sodium-coupled phosphate transporters. J Biol Chem. 2011;286:15032.
220. Gisler SM, Madjdpour C, Bacic D, et al. PDZK1: II. An anchoring site for the PKA-binding protein D-AKAP2 in renal proximal tubular cells. Kidney Int. 2003;64:1746.
221. Gisler SM, Pribanic S, Bacic D, et al. PDZK1: I. A major scaffolder in brush borders of proximal tubular cells. Kidney Int. 2003;64:1733.
http://www.ncbi.nlm.nih.gov/pubmed/14531807
222. Gisler SM, Stagljar I, Traebert M, et al. Interaction of the type IIa Na/Pi cotransporter with PDZ proteins. J Biol Chem. 2001;276:9206.
http://www.ncbi.nlm.nih.gov/pubmed/11099500
223. Gitelman HJ, Graham JB, Welt LG. A new familial disorder characterized by hypokalemia and hypomagnesemia. Trans Assoc Am Physicians. 1966;79:221.
http://www.ncbi.nlm.nih.gov/pubmed/5929460
224. Glikman RM. Malabsorption: pathophysiology and diagnosis. In: Wyngaarden JB, Smith LHJ, eds. Cecil's Textbook of Medicine. Philadelphia: Saunders; 1985:710.
225. Glorieux FH, Marie PJ, Pettifor JM, et al. Bone response to phosphate salts, ergocalciferol, and calcitriol in hypophosphatemic vitamin D-resistant rickets. N Engl J Med. 1980;303:1023.
226. Gogusev J, Duchambon P, Stoermann-Chopard C, et al. De novo expression of transforming growth factor-alpha in parathyroid gland tissue of patients with primary or secondary uraemic hyperparathyroidism. Nephrol Dial Transplant.1996;11:2155.
227. Gold LW, Massry SG, Arieff AI, et al. Renal bicarbonate wasting during phosphate depletion: A possible cause of altered acid-base homeostasis in hyperparathyroidism. J Clin Invest. 1973;52:2556.
http://www.ncbi.nlm.nih.gov/pubmed/4729049
228. Gold LW, Massry SG, Friedler RM. Effect of phosphate depletion on renal tubular reabsorption of glucose. J Lab Clin Med. 1977;89:554.
http://www.ncbi.nlm.nih.gov/pubmed/839113
229. Golden P, Mazey R, Greenwalt A, et al. Vitamin D: A direct effect on the parathyroid gland. Miner Electrolyte Metab. 1979;2:1.
230. Goldfarb S, Westby GR, Goldberg M, et al. Renal tubular effects of chronic phosphate depletion. J Clin Invest. 1977;59:770.
http://www.ncbi.nlm.nih.gov/pubmed/856868
231. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000;342:1478.
232. Goodyer PR, Kachra Z, Bell C, et al. Renal tubular cells are potential targets for epidermal growth factor. Am J Physiol. 1988;255:1191.
http://www.ncbi.nlm.nih.gov/pubmed/3264462
233. Gowen LC, Petersen DN, Mansolf AL, et al. Targeted disruption of the osteoblast/osteocyte factor 45 gene (OF45) results in increased bone formation and bone mass. J Biol Chem. 2003;278:1998.
http://www.ncbi.nlm.nih.gov/pubmed/12421822
234. Graf H, Kovarik J, Stummvoll HK, et al. Handling of phosphate by the transplanted kidney. Proc Eur Dial Transplant Assoc. 1979;16:624.
http://www.ncbi.nlm.nih.gov/pubmed/398523
235. Granam LACJJ, Burger ASV. Gastrointestinal absorption and excretion of Mg^{28} in man. Metabolism. 1960;9:646.
236. Gray RW, Wilz DR, Caldas AE, et al. The importance of phosphate in regulating plasma 1,25$(OH)_2$ vitamin D levels in humans: Studies in healthy subjects, in calcium-stone formers and in patients with primary hyperparathyroidism. J Clin Endocrinol Metab. 1977;45:299.
http://www.ncbi.nlm.nih.gov/pubmed/885994
237. Green J, Debby H, Lederer E, et al. Evidence for a PTH-independent humoral mechanism in post-transplant hypophosphatemia and phosphaturia. Kidney Int. 2001;60:1182.
http://www.ncbi.nlm.nih.gov/pubmed/11532115
238. Grill V, Martin TJ. eds. Parathyroid hormone-related protein as a cause of hypercalcemia in malignancy. In: Bilezikian JP, Marcus R, Levine MA, eds. The Parathyroids: Basic and Clinical Concepts. New York: Raven Press; 1994:295.
239. Gucalp R, Theriault R, Gill I, et al. Treatment of cancer-associated hypercal-cemia: Double-blind comparison of rapid and slow intravenous infusion regimens of pamidronate disodium and saline alone. Arch Intern Med. 1994;154:1935.
http://www.ncbi.nlm.nih.gov/pubmed/8074597
240. Guerin AP, London GM, Marchais SJ, et al. Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant. 2000;15:1014.
http://www.ncbi.nlm.nih.gov/pubmed/10862640
241. Guignard JP, Jones NF, Barraclough MA. Effect of brief hypercalcemia on free water reabsorption during solute diuresis: Evidence for impairment of sodium transport in Henle's loop. Clin Sci. 1970;39:337.
http://www.ncbi.nlm.nih.gov/pubmed/5459162
242. Gunther W, Luchow A, Cluzeaud F, et al. C1C-5, the chloride channel mutated in Dent's disease, colocalizes with the proton pump in endocytotically active kidney cells. Proc Natl Acad Sci U S A. 1998;95:8075.
243. Guntupalli J, Eby B, Lau K. Mechanism for the phosphaturia of NH_4Cl: Dependence on acidemia but not on diet PO_4 or PTH. Am J Physiol. 1982;242: F552–F560.
http://www.ncbi.nlm.nih.gov/pubmed/6282142
244. Guo R, Liu S, Spurney RF, et al. Analysis of recombinant Phex: an endo-peptidase in search of a substrate. Am J Physiol Endocrinol Metab 2001;281:837.
http://www.ncbi.nlm.nih.gov/pubmed/11551862
245. Gyory AZ, Stewart JH, George CR, et al. Renal tubular acidosis, due to hyperkalemia, hypercalcemia, disordered citrate metabolism and other tubular dysfunction following human renal transplantation. Q J Med. 1969;38:231.
http://www.ncbi.nlm.nih.gov/pubmed/4889204
246. Haas JA, Larson MV, Marchand GR, et al. Phosphaturic effect of furosemide: role of TH and carbonic anhydrase. Am J Physiol. 1977;232:F105–F110.
247. Habener JF, Potts JT Jr. Regulation of parathyroid hormone secretion in vitro. Quantitative aspects of calcium and magnesium ion control. Endocrinology. 1971;88:1477.
http://www.ncbi.nlm.nih.gov/pubmed/5572974
248. Habener JF, Potts JT Jr. Relative effectiveness of magnesium and calcium on the secretion and biosynthesis of parathyroid hormone in vitro. Endocrinology. 1976;98:197.
http://www.ncbi.nlm.nih.gov/pubmed/1248443
249. Habener JL, Mahaffey JE. Osteomalacia and disorders of vitamin D metabo-lism. Ann Rev Med. 1978;29:327.
http://www.ncbi.nlm.nih.gov/pubmed/206185
250. Haldiman B, Goldstein DA, Akmal M. Renal function and blood levels of divalent ions in acute pancreatitis: A prospective study in 99 patients. Miner Electrolyte Metab. 1980;3:190.
251. Hamilton JW, Spierto FW, MacGregor RR. Studies on the biosynthesis in vitro of parathyroid hormone. II. The effect of calcium and magnesium on synthesis of parathyroid hormone isolated from bovine parathyroid tissue and incubation medium. J Biol Chem. 1971;246:3224.
http://www.ncbi.nlm.nih.gov/pubmed/5574397
252. Hammerman MR, Hruska KA. Cyclic AMP-dependent protein phosphorylation in canine renal brush-border membrane vesicles is associated with decreased Pi transport. J Biol Chem. 1982;257:992.
http://www.ncbi.nlm.nih.gov/pubmed/6274874
253. Haramati A, Haas JA, Knox FG. Adaptation of deep and superficial nephrons to changes in dietary phosphate intake. Am J Physiol. 1983;244:F265–F269.
254. Haramati A, Haas JA, Knox FG. Nephron heterogeneity of phosphate reabsorption: Effect of parathyroid hormone. Am J Physiol. 1984;246:F155–F158.
255. Harris BZ, Lim WA. Mechanism and role of PDZ domains in signaling complex assembly. J Cell Sci. 2001;114:3219.
http://www.ncbi.nlm.nih.gov/pubmed/11591811
256. Harris CA, Bauer PG, Chirito E, Dirks JH. Composition of mammalian glomerular filtrate. Am J Physiol. 1974;227:972.
http://www.ncbi.nlm.nih.gov/pubmed/4429147
257. Harris CA, Burnatowska MA, Seely JF. Effects of parathyroid hormone on electrolyte transport in the hampster nephron. Am J Physiol. 1979;236:342.
258. Hattenhauer O, Traebert M, Murer H, et al. Regulation of small intestinal Na-P(i) type IIb cotransporter by dietary phosphate intake. Am J Physiol. 1999;277:756.
259. Hayes G, Busch AE, Lang F, et al. Protein kinase C consensus sites and the regulation of renal Na/Pi-cotransport (NaPi-2) expressed in XENOPUS laevis oocytes. Pfugers Arch (Euro J Physiol). 1995;430:819.
260. Hebert SC, Brown EM. The scent of an ion: calcium-sensing and its roles in health and disease. Curr Opin Nephrol Hypertens. 1996;5:45.
http://www.ncbi.nlm.nih.gov/pubmed/8834161
261. Hebert SC, Culpepper RM, Andreoli TE. NaCl transport in mouse medullary thick ascending limbs: I. Functional nephron heterogeneity and ADH-stimulated NaCl co-transport. Am J Physiol. 1981;241:F412.
262. Herdman RC, Michael AF, Vernier RL, et al. Renal function and phosphorus excretion after human renal homotransplantation. Lancet. 1966;1:121.
http://www.ncbi.nlm.nih.gov/pubmed/4158953

263. Hernando N, Deliot N, Gisler SM, et al. PDZ-domain interactions and apical expression of type IIa Na/P(i) cotransporters. Proc Natl Acad Sci U S A. 2002;99:11957.
http://www.ncbi.nlm.nih.gov/pubmed/12192091
264. Hewison M, Rut AR, Kristjansson K, et al. Tissue resistance to 1,25-dihydroxyvitamin D without a mutation of the vitamin D receptor gene. Clin Endocrinol. 1993;39:663.
http://www.ncbi.nlm.nih.gov/pubmed/8287584
265. Hilfiker H, Hattenhauer O, Traebert M, et al. Characterization of a murine type II sodium-phosphate cotransporter expressed in mammalian small intestine. Proc Natl Acad Sci U S A. 1998;95:14564.
http://www.ncbi.nlm.nih.gov/pubmed/9826740
266. Hochberg Z, Weisman Y. Calcitriol-resistant rickets due to vitamin D receptor defects. Trends Endocrinol Metab 1995;6:216.
http://www.ncbi.nlm.nih.gov/pubmed/18406705
267. Hoenderop JG, Hartog A, Stuiver M, et al. Localization of the epithelial Ca^{2+} channel in rabbit kidney and intestine. J Am Soc Nephrol. 2000;11:1171.
http://www.ncbi.nlm.nih.gov/pubmed/10864572
268. Hoenderop JG, Nilius B, Bindels RJ. Molecular mechanisms of active Ca^{2+} reabsorption in the distal nephron. Ann Rev Physiol. 2002;64:529.
269. Hoenderop JG, Voets T, Hoefs S, et al. Homo- and heterotetrameric architecture of the epithelial Ca2+ channels, TRPV5 and TRPV6. EMBO J. 2003;22:776.
270. Hoenderop JGJ, vanderKemp AWCM, Hartog A, et al. Molecular identification of the apical Ca^{2+} channel in 1,25-dihydroxyvitamin D_3_responsive epithelia. J Biol Chem. 1999;274:8375.
http://www.ncbi.nlm.nih.gov/pubmed/10085067
271. Hoenderop JGJ, Willems PHGM, Bindels RJM. Toward a comprehensive molecular model of active calcium reabsorption. Am J Physiol Renal. 2000;278: F352–F360.
http://www.ncbi.nlm.nih.gov/pubmed/10710538
272. Hoffmann N, Thees M, Kinne R. Phosphate transport by isolated renal brush border vesicles. Pfugers Arch (Euro J Physiol). 1976;362:147.
http://www.ncbi.nlm.nih.gov/pubmed/4766
273. Honig PJ, Holtzapple PG. Hypocalcemic tetany following hypertonic phos-phate enemas. Clin Pediatr. 1975;14:678.
http://www.ncbi.nlm.nih.gov/pubmed/1139852
274. Hopkins T, Howard JE, Eisenberg H. Ultrafiltration studies on calcium and phosphorus in human serum. Bull Johns Hopkins Hospital. 1952;91:1.
http://www.ncbi.nlm.nih.gov/pubmed/14935475
275. Hoppe A, Metler M, Berndt TJ, et al. Effect of respiratory alkalosis on renal phosphate excretion. Am J Physiol. 1982;243:F471–F475.
276. Horton R, Biglieri EG. Effect of aldosterone on the metabolism of magnesium. J Clin Endocrinol. Metab. 1962;22:1187.
277. Horwitz MJ, Tedesco MB, Sereika SM, et al. Direct comparison of sustained infusion of human parathyroid hormone-related protein-(1-36) [hPTHrP-(1-36)] versus hPTH-(1-34) on serum calcium, plasma 1,25-dihydroxyvitamin D concentrations, and fractional calcium excretion in healthy human volunteers. J Clin Endo Metab. 2003;88:1603.
278. Howell RR. Essential fructosuria and hereditary fructose intolerance. In: Wyngaarden JB, Smith LHJ, eds. Cecil's Textbook of Medicine. Philadelphia: Saunders; 1985:1100.
279. Hruska KA, Mathew S. eds. The chronic kidney disease mineral bone disorder (CKD-MBD). Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, Philadelphia: Lippincott Williams & Wilkins, 2008.
280. Hruska KA. Pathophysiology of renal osteodystrophy. Pediatr Nephrol. 2000;14:636.
http://www.ncbi.nlm.nih.gov/pubmed/10912533
281. Hruska KA, Hammerman MR. Parathyroid hormone inhibition of phosphate transport in renal brush border vesicles from phosphate-depleted dogs. Biochim Biophys Acta. 1981;645:351.
http://www.ncbi.nlm.nih.gov/pubmed/7272293
282. Hruska KA, Mills SC, Khalifa S. Phosphorylation of renal brush border membrane vesicles of calcium uptake and membrane content of polyphos- phoinositides. J Biol Chem. 1983;258:2501.
http://www.ncbi.nlm.nih.gov/pubmed/6296149
283. Huang CL. The transient receptor potential superfamily of ion channels. J Am Soc Nephrol. 2004;15:1690.
http://www.ncbi.nlm.nih.gov/pubmed/15213256
284. Huber TB, Schmidts M, Gerke P, et al. The carboxyl terminus of Neph family members binds to the PDZ domain protein zonula occludens-1. J Biol Chem. 2003;278:13417.
http://www.ncbi.nlm.nih.gov/pubmed/12578837
285. Hugo C, Nangaku M, Shankland SJ, et al. The plasma membrane-actin linking protein, ezrin, is a glomerular epithelial cell marker in glomerulogenesis, in the adult kidney and in glomerular injury. Kidney Int. 1998;54:1934.
286. Humes HD. Regulation of intracellular calcium. Semin Nephrol. 1984; 4(2):117.
287. Humes HD, Ichikawa I, Troy JL. Influence of calcium on the determinants of glomerular ultrafiltration. Trans Assoc Am Physicians. 1977;90:228.
http://www.ncbi.nlm.nih.gov/pubmed/611661
288. Hung AY, Sheng M. PDZ domains: structural modules for protein complex assembly. J Biol Chem. 2002;277:5699.
http://www.ncbi.nlm.nih.gov/pubmed/11741967
289. Hurd TW, Gao L, Roh MH, et al. Direct interaction of two polarity complexes implicated in epithelial tight junction assembly. Nat Cell Biol. 2003;5:137.
http://www.ncbi.nlm.nih.gov/pubmed/12545177
290. Ichikawa S, Lyles KW, Econs MJ. A novel GALNT3 mutation in a pseudoautosomal dominant form of tumoral calcinosis: Evidence that the disorder is autosomal recessive. J Clin Endocrinol Metab. 2005;90:2420–2423.
291. Ichikawa S, Imel EA, Kreiter ML, et al. A homozygous missense mutation in human KLOTHO causes severe tumoral calcinosis. J Clin Invest. 2007;117:2684–2691.
http://www.ncbi.nlm.nih.gov/pubmed/18094491
292. Imai M. Calcium transport across the rabbit thick ascending limb of Henle's loop perfused in vitro. Pfugers Arch. 1978;374:255.
http://www.ncbi.nlm.nih.gov/pubmed/566905
293. Ireland AW, Hornbrook HW, Neale FC. The crystalline lens in chronic surgical hypoparathyroidism. Arc Intern Med. 1968;122:408.
http://www.ncbi.nlm.nih.gov/pubmed/5687928
294. Ishibashi K, Imai M. Prospect of a stanniocalcin endocrine/paracrine system in mammals. Am J Physiol Renal Physiol. 2002;282:367.
295. Ishibashi K, Miyamoto K, Taketani Y, et al. Molecular cloning of a second human stanniocalcin homologue (STC2). Biochem Biophys Res Commun. 1998;250:252.
http://www.ncbi.nlm.nih.gov/pubmed/9753616
296. Ito H, Sanada T, Katayama T. Indomethacin-responsive hypercalcemia. N Engl J Med. 1975;293:558.
http://www.ncbi.nlm.nih.gov/pubmed/1152883
297. Ito M, Iidawa S, Izuka M, et al. Interaction of a farnesylated protein with renal type IIa Na/Pi co-transporter in response to parathyroid hormone and dietary phosphate. Biochem J. 2004;377:607.
http://www.ncbi.nlm.nih.gov/pubmed/14558883
298. Jacob HS, Amsden T. Acute hemolytic anemia and rigid red cells in hypophosphatemia. N Engl J Med. 1971;285:1446.
http://www.ncbi.nlm.nih.gov/pubmed/5122895
299. Jaffe BM, Parker CW, Philpott GW. Immunochemical measurement of prostaglandin or prostaglandin-like activity from normal and neoplastic cultured tissue. Surg Forum. 1971;22:90.
http://www.ncbi.nlm.nih.gov/pubmed/5121477
300. Jain A, Fedarko NS, Collins MT, et al. Serum levels of matrix extracellular phos-phoglycoprotein (MEPE) in normal humans correlate with serum phosphorus, para-thyroid hormone and bone mineral density. J Clin Endocrinol Metab. 2004;89:4158.
301. Jaureguiberry G, Carpenter TO, Forman S, et al. A novel missense mutation in SLC34A3 that causes hereditary hypophosphatemic rickets with hypercalciuria in humans identifies threonine 137 as an important determinant of sodium-phosphate cotransport in NaPi-IIc. Am J Physiol Renal Physiol. 2008;295:F371–F379.
302. Jayakumar A, Liang CT, Sacktor B. Na^+ gradient-dependent Ca^{2+} transport in rat.
303. Jencks WP. How does a calcium pump pump calcium? J Biol Chem. 1989;264:18855.
http://www.ncbi.nlm.nih.gov/pubmed/2530226
304. Jentsch TJ, Gunther W. Chloride channels: an emerging molecular picture. BioEssays. 1997;19:117.
http://www.ncbi.nlm.nih.gov/pubmed/9046241
305. Jentsch TJ, Poet M, Fuhrmann JC, et al. Physiological functions of CLC Cl^- channels gleaned from human genetic disease and mouse models. Annu Rev Physiol. 2005;67:779.
http://www.ncbi.nlm.nih.gov/pubmed/15709978
306. Jones JE, Shane SR, Jacobs WH. Magnesium balance studies in chronic alcoholism. N Y Acad Sci. 1969;162:934.
http://www.ncbi.nlm.nih.gov/pubmed/5259582
307. Jonsson KB, Zahradnik R, Larsson T, et al. Fibroblast growth factor 23 in onco-genic osteomalacia and X-linked hypophosphatemia. N Engl J Med. 2003;348:1656.
308. Jowsey J, Riggs BL. Bone changes in a patient with hypervitaminosis. J Clin Endocrinol. Metab. 1968;28:1833.
http://www.ncbi.nlm.nih.gov/pubmed/5699952

309. Juan D, Elrazak MA. Hypophosphatemia in hospitalized patients. JAMA. 1979;242:163.
http://www.ncbi.nlm.nih.gov/pubmed/448890
310. Kalbfeish JM, Lindeman RD, Ginn HE. Effects of ethanol administration on urinary excretion of magnesium and other electrolytes in alcoholic and normal subjects. J Clin Invest. 1963;42:1471.
http://www.ncbi.nlm.nih.gov/pubmed/14060991
311. Kammerman S, Canfield RE. Effect of porcine calcitonin on hypercalcemia in man. J Clin Endocrinol. 1970;31:70.
312. Karim Z, Gerard B, Bakouh N, et al. NHERF1 mutations and responsiveness of renal parathyroid hormone. NEJM. 2008;359:1128.
313. Karthikeyan S, Leung T, Ladias JA. Structural determinants of the Na+/H+ exchanger regulatory factor interaction with the beta 2 adrenergic and platelet-derived growth factor receptors. J Biol Chem. 2002;277:18973.
314. Katai K, Miyamoto K, Kishida S, et al. Regulation of intestinal Na+ -dependent phosphate co-transporters by a low-phosphate diet and 1,25- dihydroxyvitamin D3. Biochem J. 1999;343 Pt 3:705.
http://www.ncbi.nlm.nih.gov/pubmed/10527952
315. Katai K, Tanaka H, Tatsumi S, et al. Nicotinamide inhibits sodium-dependent phosphate cotransport activity in rat small intestine. Nephrol Dial Transplant. 1999;14:1195.
http://www.ncbi.nlm.nih.gov/pubmed/10344361
316. Katz CM, Tzagournis M. Chronic adult hypervitaminosis A with hypercalcemia. Metabolism. 1972;21:1171.
317. Kavanaugh MP, Miller DG, Zhang W, et al. Cell-surface receptors for gibbon ape leukemia virus and amphotropic murine retroviruses are inducible sodium-dependent phosphate symporters. Proc Natl Acad Sci U S A. 1994;91:7071.
http://www.ncbi.nlm.nih.gov/pubmed/8041748
318. Keating MJ, Sethi MR, Bodey GP. Hypocalcemia with hypoparathyroidism and renal tubular dysfunction associated with aminoglycoside therapy. Cancer. 1977;39:1410.
http://www.ncbi.nlm.nih.gov/pubmed/856439
319. Kempson SA, Lotscher M, Kaissling B, et al. Parathyroid hormone action on phosphate transporter mRNA and protein in rat renal proximal tubules. Am J Physiol. 1995;268:F784–F791.
320. Khalifa S, Mills SC, Hruska K. Stimulation of calcium uptake by parathyroid hormone in renal border membrane vesicles. J Biol Chem. 1983;258:400.
http://www.ncbi.nlm.nih.gov/pubmed/6643490
321. Kikuchi K, Ghishan FK. Phosphate transport by basolateral plasma membranes of human small intestine. Gastroenterology. 1987;93:106.
http://www.ncbi.nlm.nih.gov/pubmed/2438183
322. Kim YS, McDonald PN, Dedhar S, et al. Association of 1α,25-dihydroxyvitamin D3-occupied vitamin D receptors with cellular membrane acceptance sites. Endocrinology. 1996;137:3649.
323. Kitsiou-Tzeli S, Kolialexi A, Fryssira H, et al. Detection of 22q11.2 deletion among 139 pateints with Di George/Velo cardiofacial syndrome features. In Vivo. 2004;18:603.
324. Klahr S, Davis TA. Changes in renal function with chronic protein-calorie malnutrition. In: Mitch WE, Klahr S, eds. Nutrition and the Kidney. Boston: Little, Brown and Co; 1988:59.
325. Klahr S, Slatopolsky E. eds. Urinary phosphate and cyclic AMP in pseudohypoparathyroidism. In: Massry SG, Ritz E, Rapado A, eds. Homeostasis of Phosphate and Other Minerals. New York: Plenum; 1977:173.
326. Klein DC, Raisz LA. Prostaglandin stimulation of bone resorption in tissue culture. Endocrinology. 1970;86:1436.
327. Klock JC, Williams HE, Mentzer WC. Hemolytic anemia and somatic cell dysfunction in severe hypophosphatemia. Arch Intern Med. 1974;134:360.
http://www.ncbi.nlm.nih.gov/pubmed/4843204
328. Knochel JP. The pathophysiology and clinical characteristics of severe hyperphosphatemia. Arch Intern Med. 1977;137:203.
http://www.ncbi.nlm.nih.gov/pubmed/836118
329. Knochel JP, Barcenas C, Cotton JR, et al. Hypophosphatemia and rhabdomyolysis. J Clin Invest. 1978;62:1240.
330. Knochel JP, Bilbrey GL, Fuller TJ. The muscle cell in chronic alcoholism: the possible role of phosphate depletion in alcoholic myopathy. Ann N Y Acad Sci. 1975;252:274.
http://www.ncbi.nlm.nih.gov/pubmed/1056729
331. Knohl SJ, Scheinman SJ. Inherited hypercalciuric syndromes: Dent's disease (CLC-5) and familial hypomagnesemia with hypercalciuria (paracellin-1). Semin Nephrol. 2004;24:55.
http://www.ncbi.nlm.nih.gov/pubmed/14730510
332. Knox FG, Osswald H, Marchand GR, et al. Phosphate transport along the nephron. Am J Physiol. 1977;233:F261–F268.
333. Knox FG, Preiss J, Kim JK, et al. Mechanism of resistance to the phosphaturic effect of the parathyroid hormone in the hamster. J Clin Invest. 1977;59:675.
http://www.ncbi.nlm.nih.gov/pubmed/14974
334. Kocher O, Yesilaltay A, Cirovic C, et al. Targeted disruption of the PDZK1 gene in mice causes tissue-specific depletion of the high density lipoprotein receptor scavenger receptor class B type I and altered lipoprotein metabolism. J Biol Chem. 2003;278:52820.
http://www.ncbi.nlm.nih.gov/pubmed/14551195
335. Koffer A, Friedler RM, Massry SG. Acute renal failure due to nontraumatic rhabdomyolysis. Ann Intern Med. 1976;85:23.
http://www.ncbi.nlm.nih.gov/pubmed/937919
336. Kong Y-Y, Yoshida H, Sarosi I, et al. OPGL is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature. 1999;397:315.
http://www.ncbi.nlm.nih.gov/pubmed/9950424
337. Kono N, Kuwajima M, Tarui S. Alteration of glycolytic intermediary metabolism in erythrocytes during diabetic ketoacidosis and its recovery phase. Diabetes. 1981;30:346.
http://www.ncbi.nlm.nih.gov/pubmed/6451463
338. Konrad M, Schlingmann KP, Gudermann T. Insights into the molecular nature of magnesium homeostasis. Am J Physiol. Renal Physiol. 2003;286:F599–F605.
339. Koulen P, Cai Y, Geng L, et al. Polycystin-2 is an intracellular calcium release channel. Nature Cell Biol. 2002;4:191.
http://www.ncbi.nlm.nih.gov/pubmed/11854751
340. Kreisberg RA. Phosphorus deficiency and hypophosphatemia. Hosp Pract. 1977;12:121.
http://www.ncbi.nlm.nih.gov/pubmed/402311
341. Kretz J, Sommer G, Boland R, et al. Lack of involvement of sarcoplasmic reticulum in myopathy of acute phosphorus depletion. Klin Wochenschr. 1980;58:833.
http://www.ncbi.nlm.nih.gov/pubmed/7453090
342. Kreusser WJ, Kurokawa K, Aznar E. Effect of phosphate depletion on magnesium homeostasis in rats. J Clin Invest. 1978;61:573.
http://www.ncbi.nlm.nih.gov/pubmed/641138
343. Kulkarni RN, Roper MG, Dahlgren G, et al. Islet secretory defect in insulin receptor substrate 1 null mice is linked with reduced calcium signaling and expression of sarco(endo)plasmic reticulum Ca2+ -ATPase (SERCA)-2b and -3. Diabetes. 2004;1953:1517.
344. Kumar V, Bustin SA, McKay IA. Transforming growth factor alpha. Cell Biol Int. 1995;19:373.
http://www.ncbi.nlm.nih.gov/pubmed/7640654
345. Kuntziger HE, Amiel C, Couette S, et al. Localization of parathyroid-hormone-independent sodium bicarbonate inhibition of tubular phosphate reabsorption. Kidney Int. 1980;17:749.
http://www.ncbi.nlm.nih.gov/pubmed/7412108
346. Kurnik BR, Hruska KA. Effects of 1,25-dihydroxycholecalciferol on phosphate transport in vitamin D-deprived rats. Am J Physiol. 1984;247:F177–F184.
347. Kurz P, Monier-Faugere M-C, Bognar B, et al. Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. Kidney Int. 1994;46:855–861.
http://www.ncbi.nlm.nih.gov/pubmed/7996807
348. L'Estrange JL, Axford RFE. A study of magnesium and calcium metabolism in lactating ewes semi-purified diet low in magnesium. J Agric Sci. 1964;62:353.
349. Lacey DL, Timms E, Tan H-L, et al. Osteoprotegrin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell. 1998;93:165.
http://www.ncbi.nlm.nih.gov/pubmed/9568710
350. Lambert PP, Corvilan J. eds. Site of action of parathyroid hormone and role of growth hormone in phosphate excretion. In: Williams PC, eds. Hormones and the Kidney (Memoirs of the Society of Endocrinology, No. 13). New York: Academic Press; 1963:130.
351. Lanzano L, Lei T, Okamura K, et al. Differential modulation of the molecular dynamics of the type IIa and IIc sodium phosphate cotransporters by parathyroid hormone. Am J Physiol Cell Physiol. 2011;301:C850–C861.
352. Larsson L, Rebel K, Sorbo B. Severe hypophosphatemia—a hospital survey. Acta Med Scand. 1983;214:221.
http://www.ncbi.nlm.nih.gov/pubmed/6660029
353. Larsson T, Marsell R, Schipani E, et al. Transgenic mice expressing fibroblast growth factor 23 under the control of the alpha1(I) collagen promoter exhibit growth retardation, osteomalacia, and disturbed phosphate homeostasis. Endocrinology. 2004;145:3087.
http://www.ncbi.nlm.nih.gov/pubmed/14988389
354. Larsson T, Zahradnik R, Lavigne J, et al. Immunohistochemical detection of FGF-23 protein in tumors that cause oncogenic osteomalacia. Eur J Endocrinol. 2003;148:269.
http://www.ncbi.nlm.nih.gov/pubmed/12590648

355. Laspa E, Bastepe M, Juppner H, et al. Phenotypic and molecular genetic aspects of pseudohypoparathyroidism type Ib in a Greek kindred: evidence for enhanced uric acid excretion due to parathyroid hormone resistance. J Clin Endocrinol Metab. 2004;1989;5942.
356. Lassiter WE, Gottschalk CW, Mylle M. Micropuncture study of tubular reabsorption of calcium in normal rodents. Am J Physiol. 1963;204:771.
http://www.ncbi.nlm.nih.gov/pubmed/13949504
357. Lau YK, Goldfarb S, Goldberg M. Effects of phosphate administration on tubular calcium transport. J Lab Clin Med. 1982;99:317.
http://www.ncbi.nlm.nih.gov/pubmed/7057059
358. Le Grimellec C, Roinel N, Morel F. Simultaneous Mg, Ca, P, K and Cl analysis in rat tubular fuid. IV During acute phosphate plasma loading. Pfugers Arch (Euro J Physiol). 1974;346:189.
http://www.ncbi.nlm.nih.gov/pubmed/4856413
359. Lederer ED, Khundmiri SJ, Weinman EJ. Role of NHERF-1 in regulation of the activity of Na-K ATPase and sodium-phosphate co-transport in epithelial cells. J Am Soc Nephrol. 2003;14:1711.
http://www.ncbi.nlm.nih.gov/pubmed/12819230
360. Lederer ED, Sohi SS, McLeish KR. Parathyroid hormone stimulates extra-cellular signal-regulated kinase (ERK) activity through two independent signal transduction pathways: role of ERK in sodium-phosphate cotransport. J Am Soc Nephrol. 2000;11:222.
http://www.ncbi.nlm.nih.gov/pubmed/10665929
361. Lee JC, Catanzaro A, Parthemore JG. Hypercalcemia in disseminated coccidioidomycosis. N Engl J Med. 1977;297:431.
http://www.ncbi.nlm.nih.gov/pubmed/882114
362. LeGrimellec C, Roinel N, Morel F. Simultaneous Mg, Ca, P, K, Na, and Cl analysis in rat tubular fuid: I. During perfusion of either insulin or ferrocyanide. Pfugers Arch. 1973;340:181.
http://www.ncbi.nlm.nih.gov/pubmed/4736756
363. Lennquist S, Lindell B, Nordstrom H, et al. Hypophosphatemia in severe burns: A prospective study. Acta Chir Scand. 1979;145:1.
http://www.ncbi.nlm.nih.gov/pubmed/433511
364. Lentz RD, Brown DM, Kjellstrand CM. Treatment of severe hypophosphatemia. Ann Intern Med. 1978;89:941.
http://www.ncbi.nlm.nih.gov/pubmed/102230
365. Levi J, Massry SG, Coburn JW. Hypocalcemia in magnesium depleted dogs: Evidence for reduced responsiveness to parathyoid hormone and relative failure of parathyroid gland function. Metabolism. 1974;23:323.
http://www.ncbi.nlm.nih.gov/pubmed/4817361
366. Levi M. Post-transplant hypophosphatemia. Kidney Int. 2001;59:2377.
http://www.ncbi.nlm.nih.gov/pubmed/11380848
367. Levi M. Role of PDZ domain-containing proteins and ERM proteins in regulation of renal function and dysfunction. J Am Soc Nephrol. 2003;14:1949.
http://www.ncbi.nlm.nih.gov/pubmed/12819256
368. Levi M, Kempson SA, Lotscher M, et al. Molecular regulation of renal phosphate transport. J Membrane Biology. 1996;154:1.
http://www.ncbi.nlm.nih.gov/pubmed/8881022
369. Levi M, Lotscher M, Sorribas V, et al. Cellular mechanisms of acute and chronic adaptation of rat renal P(i) transporter to alterations in dietary P(i). Am J Physiol. 1994;267:F900–F908.
370. Levi M, Shayman JA, Abe A, et al. Dexamethasone modulates rat renal brush border membrane phosphate transporter mRNA and protein abundance and glycosphingolipid composition. J Clin Invest. 1995;96:207.
http://www.ncbi.nlm.nih.gov/pubmed/7615789
371. Levi M. Novel NaPi-2c mutations that cause mistargeting of NaPi-2c protein and uncoupling of Na-Pi cotransport cause HHRH. Am J Physiol Renal Physiol. 2008;295:F369–F370.
372. Levi M, Breusegem S. Renal phosphate-transporter regulatory proteins and nephrolithiasis. N Engl J Med. 2008;359:1171.
http://www.ncbi.nlm.nih.gov/pubmed/18784108
373. Levine BS, Kleeman CR. Hypophosphatemia and hyperphosphatemia: clini-cal and pathophysiologic aspects. In: Maxwell MH, Kleeman CR, eds. Clinical Disorders of Fluid and Electrolyte Metabolism. New York: McGraw-Hill; 1994:1040.
374. Levine MA. Resistance to multiple hormones in patients with pseudohypoparathyroidism: Association with deficient activity of guanine nucleotide regulatory protein. Am J Med. 1983;74:545.
http://www.ncbi.nlm.nih.gov/pubmed/6301273
375. Levine MA, Jap TS, Mauseth RS, et al. Activity of the stimulatory guanine nucleotide-binding protein is reduced in erythrocytes from patients with pseu-dohypoparathyroidism and pseudopseudohypoparathyroidism: Biochemical, endocrine, and genetic analysis of Albright's hereditary osteodystrophy in six kindreds. J Clin Endocrinol. Metab. 1986;62:497.
http://www.ncbi.nlm.nih.gov/pubmed/3003142
376. Levine MA, Schwindinger WF, Downs RW Jr, Moses AM. Pseudohypoparathyroidism: Clinical, biochemical, and molecular features. In: Bilezikian JP, Marcus R, Levine MA, eds. The Parathyroids: Basic and Clinical Concepts. New York: Raven Press; 1994:781.
377. Levitt MF, Halpern MH, Polimeros DP. The effect of abrupt changes in plasma calcium concentrations on renal function and electrolyte excretion in man and monkey. J Clin Invest. 1958;37:294.
http://www.ncbi.nlm.nih.gov/pubmed/13513760
378. Levy LA. Severe hypophosphatemia as a complication of the treatment of hypothermia. Arch Intern Med. 1980;140:128.
http://www.ncbi.nlm.nih.gov/pubmed/7352789
379. Levy-Litan V, Hershkovitz E, Avizov L, et al. Autosomal-recessive hypophosphatemic rickets is associated with an inactivation mutation in the ENPP1 gene. Am J Hum Genet. 2010;86:273.
http://www.ncbi.nlm.nih.gov/pubmed/20137772
380. Li HY, Dai LJ, Quamme GA. Effect of chemical hypoxia on intracellular ATP and cytosolic levels. J Lab Clin Med. 1993;122:232.
http://www.ncbi.nlm.nih.gov/pubmed/8409702
381. Li X, Yang HY, Giachelli CM. Role of the sodium-dependent phosphate cotransporter, Pit-1, in vascular smooth muscle cell calcification. Circ Res. 2006;98:905–912.
http://www.ncbi.nlm.nih.gov/pubmed/16527991
382. Li YC, Amling M, Pirro AE, et al. Normalization of mineral ion homeostasis by dietary means prevents hyperparathyroidism, rickets, and osteomalacia, but not alopecia in vitamin D receptor-ablated mice. Endocrinology. 1998;139:4391.
http://www.ncbi.nlm.nih.gov/pubmed/9751523
383. Li YC, Pirro AE, Amling M, et al. Targeted ablation of the vitamin D receptor: An animal model of vitamin D-dependent rickets type II with alopecia. Proc Natl Acad Sci U S A. 1997;94:9831.
http://www.ncbi.nlm.nih.gov/pubmed/9275211
384. Liang CT, Barnes J, Cheng L, et al. Effects of $1,25(OH)_2D_3$ administered in vivo on phosphate uptake by isolated chick renal cells. Am J Physiol. 1982;242:C312–C318.
385. Liberman UA, Eil C, Marx SJ. Resistance of 1,25 dihydroxyvitamin D. Associated with heterogeneous defects in cultured skin fibroblasts. J Clin Invest. 1983;71:192.
386. Lichtenstein L. Polyostotic fibrous dysplasia. Arch Surg. 1938;36:874.
387. Lichtenstein L, Jaffe HL. Fibrous dysplasia of bone: a condition affecting one, several or many bones, the graver case of which may present abnormal pigmentation of skin, premature sexual development, hyperthyroidism and still other extraskeletal abnormalities. Arch Pathol. 1942;33:777.
388. Lichtman MA, Miller DR, Cohen J, Waterhouse C. Reduced red cell glycolysis, 2,3-diphosphoglycerate and adenosine triphosphate concentration and increased hemoglobin-oxygen affinity caused by hypophosphatemia. Ann Intern Med. 1971;74:562.
http://www.ncbi.nlm.nih.gov/pubmed/4994546
389. Liedtke CM, Yun CH, Kyle N, et al. Protein kinase C epsilon-dependent regulation of cystic fibrosis transmembrane regulator involves binding to a receptor for activated C kinase (RACK1) and RACK1 binding to Na+/H+ exchange regulatory factor. J Biol Chem. 2002;277:22925.
http://www.ncbi.nlm.nih.gov/pubmed/11956211
390. Lipschitz MD, Stein JH. Renal vasoactive homrones. In: Brenner B, Rector F, eds. The Kidney. Philadelphia: Saunders; 1981:650.
391. Liu J, Nealon JG, Weinstein LS. Distinct patterns of abnormal GNAS imprinting in familial and sporadic pseudohypoparathyroidism type IB. Hum Mol Genet. 2005;1914:95.
http://www.ncbi.nlm.nih.gov/pubmed/15537666
392. Liu S, Guo R, Simpson LG, et al. Regulation of fibroblastic growth factor 23 expression but not degradation by PHEX. J Biol Chem. 2003;278:37419.
http://www.ncbi.nlm.nih.gov/pubmed/12874285
393. Liu S, Guo R, Tu Q, et al. Overexpression of Phex in osteoblasts fails to rescue the Hyp mouse phenotype. J Biol Chem. 2002;277:3686.
http://www.ncbi.nlm.nih.gov/pubmed/11713245
394. Lloyd SE, Pearce SHS, Fisher SE, et al. A common molecular basis for three inherited kidney stone diseases. Nature. 1996;379:445.
http://www.ncbi.nlm.nih.gov/pubmed/8559248
395. Loffing J, Loffing-Cueni D, Valderrabano V, et al. Distribution of transcellular calcium and sodium transport pathways along mouse distal nephron. Am J Phys (Renal). 2001;291:F1021–F1027.
396. Loffing J, Lotscher M, Kaissling B, et al. Renal Na/H exchanger NHE-3 and Na-PO4 cotransporter NaPi-2 protein expression in glucocorticoid excess and deficient states. J Am Soc Nephrol. 1998;9:1560.
http://www.ncbi.nlm.nih.gov/pubmed/9727362

397. London GM, Dannier B, Marchais SJ, et al. Calcification of the aortic valve in the dialyzed patient. J Am Soc Nephrol. 2000;11:778.
http://www.ncbi.nlm.nih.gov/pubmed/10752538
398. London GM, Guerin AP, Marchais SJ, et al. Arterial media calcification in end-stage renal diseases: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant. 2003;18:1731.
399. London GM, Marty C, Marchais SJ, et al. Arterial calcifications and bone histomorphometry in end-stage renal disease. J Am Soc Neph. 2004;15:1943.
http://www.ncbi.nlm.nih.gov/pubmed/15213285
400. Lorenz-Depiereux B, Bastepe M, et-Pages A, et al. DMP1 mutations in autosomal recessive hypophosphatemia implicate a bone matrix protein in the regulation of phosphate homeostasis. Nat Genet. 2006;38:1248.
http://www.ncbi.nlm.nih.gov/pubmed/17033625
401. Lorenz-Depiereux B, Schnabel D, Tiosano D, et al. Loss-of-function ENPP1 mutations cause both generalized arterial calcification of infancy and autosomal-recessive hypophosphatemic rickets. Am J Hum Genet. 2010;86:267.
http://www.ncbi.nlm.nih.gov/pubmed/20137773
402. Lotscher M, Kaissling B, Biber J, et al. Role of microtubules in the rapid regulation of renal phosphate transport in response to acute alterations in dietary phosphate content. J Clin Invest. 1997;99:1302.
403. Lotscher M, Wilson P, Nguyen S, et al. New aspects of adaptation of rat renal Na-Pi cotransporter to alterations in dietary phosphate. Kidney Int. 1996;49:1012.
http://www.ncbi.nlm.nih.gov/pubmed/8691717
404. Lotz M, Ney R, Bartter FC. Osteomalacia and debility resulting from phosphorus depletion. Trans Ass Amer Physicians. 1964;77:281.
http://www.ncbi.nlm.nih.gov/pubmed/14275429
405. Lotz M, Zisman E, Bartter FC. Evidence for a phosphorus-depletion syndrome in man. N Engl J Med. 1968;278:409.
http://www.ncbi.nlm.nih.gov/pubmed/5636663
406. Lu M, Wagner GF, Renfro JL. Stanniocalcin stimulates phosphate reabsorption by founder renal proximal tubule in primary culture. Am J Physiol. 1994;267:1356.
407. Lufkin EG, Kumar R, Heath H III. Hyperphosphatemic tumoral calcinosis: effects of phosphate depletion on vitamin D metabolism, and of acute hypocalcemia on parathyroid hormone secretion and action. J Clin Endocrinol Metab. 1983;56:1319.
408. Lufkin EG, Wilson DM, Smith LH, et al. Phosphorus excretion in tumoral calcinosis: Response to parathyroid hormone and acetazolamide. J Clin Endocrinol Metab. 1980;50:648.
http://www.ncbi.nlm.nih.gov/pubmed/7364922
409. Lufkin EG, Wilson DM, Smith LH, et al. Phosphorus excretion in tumoral calcinosis: response to parathyroid hormone and acetazolamide. J Clin Endocrinol Metab. 1980;50:648.
http://www.ncbi.nlm.nih.gov/pubmed/7364922
410. Lyles KW, Burkes EJ, Ellis GJ, et al. Genetic transmission of tumoral calcinosis: autosomal dominant with variable clinical expressivity. J Clin Endocrinol Metab. 1985;60:1093.
411. Macefield G, Burke D. Parasthesiae and tetany induced by voluntary hyperventilation: Increased excitability of human cutaneous and motor axons. Brain. 1991;114:527.
http://www.ncbi.nlm.nih.gov/pubmed/2004255
412. MacManus J, Heaton FW. The influence of magnesium in calcium release from bone in vitro. Biochim Biophys Acta. 1970;215:360.
http://www.ncbi.nlm.nih.gov/pubmed/5503391
413. Madsen KL, Tavernini MM, Yachimec C, et al. Stanniocalcin: a novel protein regulating calcium and phosphate transport across mammalian intestine. Am J Physiol. 1998;274:96.
414. Magagnin S, Werner A, Markovich D, et al. Expression cloning of human and rat renal cortex Na/Pi cotransport. Proc Natl Acad Sci U S A. 1993;90:5979.
415. Magen D, Berger L, Coady MJ, et al. A loss-of-function mutation in NaPi-IIa and renal fanconi's syndrome. N Engl J Med. 2010;362:1102.
416. Magyar CE, White KE, Rojas R, et al. Plasma membrane Ca2+ -ATPase and NCX1 Na+/Ca2+ exchanger expression in distal convoluted tubule cells. Am J Phys (Renal). 2002;283:F29-F40.
417. Mahon MJ, Donowitz M, Yun CC, et al. Na(+)/H(+) exchanger regulatory factor 2 directs parathyroid hormone 1 receptor signalling. Nature. 2002;417:858.
http://www.ncbi.nlm.nih.gov/pubmed/12075354
418. Mallette LE, Bilezikian JP, Heath DA. Primary hyperparathyroidism: Clinical and biochemical features. Medicine. 1974;83:127.
http://www.ncbi.nlm.nih.gov/pubmed/4361513
419. Malloy PJ, Hochberg Z, Pike JW, et al. Abnormal binding of vitamin D receptors to deoxyribonucleic acid in a kindred with vitamin D-dependent rickets, type II. J Clin Endocrinol Metab. 1989;68:263.
http://www.ncbi.nlm.nih.gov/pubmed/2537329
420. Malluche HH, Meyer-Sabellek WA, Singer FR. Evidence for a direct effect of thiazides on bone. Miner Electrolyte Metab. 1980;4:89.
421. Malluche HH, Ritz E, Lange HP. Bone histology in incipient and advanced renal failure. Kidney Int. 1976;9:355–362.
http://www.ncbi.nlm.nih.gov/pubmed/940274
422. Manitius A, Levitin H, Beck D. On the mechanism of impairment of renal concentrating ability in hypercalcemia. J Clin Invest. 1960;39:693.
http://www.ncbi.nlm.nih.gov/pubmed/14420648
423. Mann JB, Alterman S, Hills AG. Albright's hereditary osteodystrophy comprising pseudohypoparathyroidism. Ann Intern Med. 1962;36:315.
424. Mantovani G, Bondioni S, Locatelli M, et al. Biallelic expression of the Gs{alpha} gene in human bone and adipose tissue. J Clin Endocrinol Metab. 2004;1989;6316.
425. Mantovani G, de Sanctis L, Barbieri AM, et al. Pseudohypoparathyroidism and GNAS epigenetic defects: clinical evaluation of Albright hereditary osteodys-trophy and molecular analysis in 40 patients. J Clin Endocrinol Metab. 2010;95:651.
http://www.ncbi.nlm.nih.gov/pubmed/20061437
426. Markowitz GS, Stokes MB, Radhakrishnan J, et al. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. J Am Soc Nephrol. 2005;16:3389.
http://www.ncbi.nlm.nih.gov/pubmed/16192415
427. Marx SJ, Spiegel AM, Brown EM. Divalent cation metabolism: Familial hypocalciuric hypercalcemia versus typical primary hyperparathyroidism. Am J Med. 1978;65:235.
http://www.ncbi.nlm.nih.gov/pubmed/686009
428. Marx SJ, Stock JL, Attie MF. Familial hypocalciuric hypercalcemia: Recognition among patients referred after unsuccessful parathyroid exploration. Ann Intern Med. 1980;92:351.
http://www.ncbi.nlm.nih.gov/pubmed/7356229
429. Massari PU. Disorders of bone and mineral metabolism after renal transplantation. Kidney Int. 1997;52:1412.
http://www.ncbi.nlm.nih.gov/pubmed/9350667
430. Massry SG, Arieff AI, Coburn JW, et al. Divalent ion metabolism in patients with acute renal failure: studies on the mechanism of hypocalcemia. Kidney Int. 1974;5:437.
431. Massry SG, Coburn JW, Chapman LW, et al. Effect of NaCl infusion on urinary Ca^{++} and Mg^{++} during reduction in their filtered loads. Am J Physiol. 1967;213:1218.
432. Massry SG, Coburn JW, Kleeman CR. Renal handling of magnesium in the dog. Am J Physiol. 1969;216:1460.
http://www.ncbi.nlm.nih.gov/pubmed/5786732
433. Massry SG, Mueller E, Silverman AG. Inorganic phosphate treatment of hypercalcemia. Intern Med 1968;12:307.
http://www.ncbi.nlm.nih.gov/pubmed/5645701
434. Mathew S, Tustison KS, Sugatani T, et al. The mechanism of phosphorus as a cardiovascular risk factor in chronic kidney disease. J Am Soc Nephrol. 2008;19:1092–1105.
http://www.ncbi.nlm.nih.gov/pubmed/18417722
435. Matzner Y, Prococimer M, Polliack A, et al. Hypophosphatemia in a patient with lymphoma in leukemic phase. Arch Intern Med. 1981;141:805.
http://www.ncbi.nlm.nih.gov/pubmed/7016060
436. Maudsley S, Zamah AM, Rahman N, et al. Platelet-derived growth factor receptor association with Na(+)/H(+) exchanger regulatory factor potentiates receptor activity. Mol Cell Biol. 2000;20:8352.
http://www.ncbi.nlm.nih.gov/pubmed/11046132
437. Mayock RL, Bertrand P, Morrison CE. Manifestations of sarcoidosis: Analysis of 145 patients, with review of nine selected from the literature. Am J Med. 1963;35:67.
http://www.ncbi.nlm.nih.gov/pubmed/14046006
438. McCarty NA, O'Neil RG. Dihydropyridine-sensitive cell volume regulation in proximal tubule: the calcium window. Am J Physiol. 1990;259:950.
http://www.ncbi.nlm.nih.gov/pubmed/2260687
439. McCarty NA, O'Neil RG. Calcium-dependent control of volume regulation in renal proximal cells. II. Roles of dihydropyridine-sensitive and insensitive Ca^{2+} entry pathways. J Membr Biol. 1991;123:161.
http://www.ncbi.nlm.nih.gov/pubmed/1659641
440. McCarty NA, O'Neil RG. Calcium-dependent control of volume regulation in renal proximal cells. I. Swelling-activated Ca^{2+} entry and release. J Membr Biol. 1991;123:149.
http://www.ncbi.nlm.nih.gov/pubmed/1659640
441. McConnell TH. Fatal hypocalcemia from phosphate absorption from laxative preparation. JAMA. 1971;216:147.
http://www.ncbi.nlm.nih.gov/pubmed/5107894

442. McCormick CC. Passive diffusion does not play a major role in the absorption of dietary calcium in normal adults. J Nutr. 2002;132:3428.
http://www.ncbi.nlm.nih.gov/pubmed/12421863
443. McCune DJ, Bruch H. Progress in pediatrics: osteodystrophia fibrosa. Am J Dis Child. 1937;54:806.
444. McMillan DE, Freeman RB. The milk alkali syndrome: A study of the acute disorder with comments on the development of the chronic condition. Medicine. 1965;44:485.
http://www.ncbi.nlm.nih.gov/pubmed/5851468
445. McPhaul MJ, Marcelli M, Zoppi S, et al. Genetic basis of endocrine disease. 4. The spectrum of mutations in the androgen receptor gene that causes androgen resistance. J Clin Endocrinol Metab. 1993;76:17.
http://www.ncbi.nlm.nih.gov/pubmed/8421085
446. Meintzer RB, Steenbock H. Vitamin D and magnesium absorption. J Nutr. 1955;56:285.
http://www.ncbi.nlm.nih.gov/pubmed/14392508
447. Mendelsoh JH, Barnes B, Mayman C. The determination of exchangeable magnesium in alcoholic patients. Metabolism. 1965;14:88.
http://www.ncbi.nlm.nih.gov/pubmed/14252347
448. Mercado A, Slatopolsky E, Klahr S. On the mechanisms responsible for the phosphaturia of bicarbonate administration. J Clin Invest. 1975;56:1386.
449. Miller ER, Ullrey DE, Zutaut CL. Effect of dietary vitamin D2 levels upon calcium, phosphorus and magnesium balance. J Nutr. 1965;85:255.
450. Miller ER, Ullrey DE, Zutaut CL. Magnesium requirement of the baby pig. J Nutr. 1965;85:13.
http://www.ncbi.nlm.nih.gov/pubmed/14256997
451. Miller MJ, Frame B, Poyanski A. Branchial anomalies in idiopathic hypoparathyroidism: Branchial dysembryogenesis. Henry Ford Hosp Med J. 1972;20:3.
452. Milliner DS, Zinsmeister AR, Lieberman L, et al. Soft tissue calcification in pediatric patients with end-stage renal disease. Kidney Int. 1990;38:931.
http://www.ncbi.nlm.nih.gov/pubmed/2266678
453. Miric A, Vechio JD, Levine MA. Heterogeneous mutations in the gene encoding the alpha subunit of the stimulatory G protein of adenylyl cyclase in Albright hereditary osteodystrophy. J Clin Endocrinol Metab. 1993;76:1560.
454. Mitnick PD, Goldbarb S, Slatopolsky E, et al. Calcium and phosphate metabolism in tumoral calcinosis. Ann Intern Med. 1980;92:482.
http://www.ncbi.nlm.nih.gov/pubmed/6244768
455. Mitnick PD, Goldfarb S, Slatopolsky E, et al. Calcium and phosphate metabolism in tumoral calcinosis. Ann Intern Med. 1980;92:482.
http://www.ncbi.nlm.nih.gov/pubmed/6244768
456. Moe OW. Scaffolds: Orchestrating proteins to achieve concerted function. Kidney Int. 2003;64:1916.
457. Moe SM, Chertow GM, Coburn JW et al. Achieving NKF-K/DOQI™ bone metabolism and disease treatment goals with cinacalcet HCl. Kidney Int. 2005;67:760.
http://www.ncbi.nlm.nih.gov/pubmed/15673327
458. Moorhead JF, Wills MR, Ahmed KY, et al. Hypophosphataemic osteomalacia after cadaveric renal transplantation. Lancet. 1974;1:694.
http://www.ncbi.nlm.nih.gov/pubmed/4132420
459. Morel F. Sites of hormone action in the mammalian nephron. Am J Physiol. 1981;240:F159.
460. Morel F, Chabardes D, Imbert M. Functional segmentation of the rabbit distal tubule by microdetermination of hormone dependent adenylate cyclase activity. Kidney Int. 1976;9:264.
http://www.ncbi.nlm.nih.gov/pubmed/940269
461. Morel F, Roinel N, LeGrimellec C. Electron probe analysis of tubular fluid composition. Nephron. 1969;6:350.
http://www.ncbi.nlm.nih.gov/pubmed/4892997
462. Morgan DB. eds. Calcium and phosphorus transport across the intestine. In: Girdwood RM, Smith AW, eds. Malabsorption. Baltimore: Williams & Wilkins; 1969.
463. Moriniere PH, Roussel A, Tahira Y, et al. Substitution of aluminum hydroxide by high doses of calcium carbonate in patients on chronic hemodialysis: disappearance of hyperalbuminemia and equal control of hyperparathyroidism. Proc Eur Dial Transplant Assoc. 1982;19:784.
http://www.ncbi.nlm.nih.gov/pubmed/6878265
464. Moser CR, Fessel WJ. Rheumatic manifestations of hypophosphatemia. Arch Intern Med. 1974;134:674.
http://www.ncbi.nlm.nih.gov/pubmed/4370345
465. Mostellar ME, Tuttle EPJ. Effects of alkalosis on plasma concentration and urinary excretion of urinary phosphate in man. J Clin Invest. 1964;43:138.
http://www.ncbi.nlm.nih.gov/pubmed/14105225
466. Mueller B, Zhao M, Negrashov IV, et al. SERCA structural dynamics induced by ATP and calcium. Biochemistry. 2004;43:12846.
http://www.ncbi.nlm.nih.gov/pubmed/15461457
467. Muhlbauer RC, Bonjour J-P, Fleisch H. Tubular handling of Pi: localization of effects of $1,25(OH)_2D_3$ and dietary Pi in TPTX rats. Am J Physiol. 1981; 241:F123–F128.
468. Mühlbauer RC, Bonjour JP, Fleisch H. Tubular localization to dietary phosphate in rats. Am J Physiol. 1978;234:F342–F348.
469. Mulder JE, Bilezikian JP. eds. Acute management of hypercalcemia. In: Bilezikian JP, Marcus R, Levine MA, eds. The Parathyroids: Basic and Clinical Concepts. San Diego: Academic Press; 2001:729.
470. Mundy GR. Evaluation and treatment of hypercalcemia. Hosp Prac. 1994; 29:79.
471. Mundy GR, Luben RA, Raisz LG. Evidence for the secretion of an osteoclast stimulating factor in myeloma. N Engl J Med. 1974;291:1041.
http://www.ncbi.nlm.nih.gov/pubmed/4413338
472. Murer H, Forster I, Biber J. The sodium phosphate cotransporter family SLC34. Pfugers Arch. 2004;447:763.
http://www.ncbi.nlm.nih.gov/pubmed/12750889
473. Murer H, Hernando N, Forster I, et al. Regulation of Na/Pi transporter in the proximal tubule. Annu Rev Physiol. 2003;65:531.
http://www.ncbi.nlm.nih.gov/pubmed/12517995
474. Murphy E, Mandel JL. Cytosolic free calcium levels in rabbit proximal kidney tubules. Am J Physiol. 1982;242:6124.
475. Nagant de Deuxchaisnes C, Krane SM. eds. Hypoparathyroidism. In: Avioli LV, Krane SM, eds. Metabolic Bone Disease. New York: Academic Press; 1978:217.
476. Nakashima K, Zhou X, Kunkel G, et al. The novel zinc finger-containing transcription factor osterix is required for osteoblast differentiation and bone formation. Cell. 2002;108:17.
http://www.ncbi.nlm.nih.gov/pubmed/11792318
477. Naren AP, Cobb B, Li C, et al. A macromolecular complex of beta 2 adrenergic receptor, CFTR, and ezrin/radixin/moesin-binding phosphoprotein 50 is regulated by PKA. Proc Natl Acad Sci U S A. 2003;100:342.
http://www.ncbi.nlm.nih.gov/pubmed/12502786
478. Neer RM, Potts JT Jr. Medical management of hypercalcemia and hyperparathyroidism. In: DeGroot LJCGF, Martini L, eds. Endocrinology. New York: Grune & Stratton; 1979:725.
479. Nelson AE, Bligh RC, Mirams M, et al. Clinical case seminar: Fibroblast growth factor 23: a new clinical marker for oncogenic osteomalacia. J Clin Endocrinol Metab. 2003;88:4088.
480. Nemere I, Norman AW. The rapid, hormonally stimulated transport of calcium (transcaltachia). J Bone Miner Res. 1987;2:167.
http://www.ncbi.nlm.nih.gov/pubmed/3331882
481. Nicoll DA, Longoni S, Philipson KD. Molecular cloning and functional ex-pression of the cardiac sarcolemmal Na^+-Ca^{2+} exchanger. Science. 1990;250:562.
http://www.ncbi.nlm.nih.gov/pubmed/1700476
482. Nijenhuis T, Hoenderop JGJ, Van Der Kemp AWCM, et al. Localization and regulation of the epithelial Ca^{2+} channel TRPV6 in the kidney. J Am Soc Neph. 2003;14:2731.
483. Nusynowitz ML, Frame B, Kolb FO. The spectrum of the hypoparathyroid states: A classification based on physiologic principles. Medicine. 1976;55:105.
484. Nutter DO, Glenn JR. Reversible severe congestive cardiomyopathy in three cases of hypophoisphatemia. Ann Intern Med. 1983;99:275.
http://www.ncbi.nlm.nih.gov/pubmed/363007
485. O'Donovan DJ, Lotspeich WD. Activation of kidney mitochondrial glutaminase by inorganic phosphate and organic acids. Nature. 1966;212:930.
http://www.ncbi.nlm.nih.gov/pubmed/6003730
486. Ohkido I, Segawa H, Yanagida R, et al. Cloning, gene structure and dietary regulation of the type-IIc Na/Pi cotransporter in the mouse kidney. Pfugers Arch. 2003;446:106.
http://www.ncbi.nlm.nih.gov/pubmed/12690469
487. Ohkido I, Yokoyama K, Kagami S, et al. The hypothesis that bone turnover influences FGF23 secretion. Kidney Int. 2010;77:743.
http://www.ncbi.nlm.nih.gov/pubmed/20354552
488. Olgaard K, Madsen S, Lund B, et al. Pathogenesis of hypophosphatemia in kidney nograft recipients: a controlled trial. Adv Exp Med Biol. 1980;128:255.
http://www.ncbi.nlm.nih.gov/pubmed/6999856
489. Olsen HS, Cepeda MA, Zhang QQ, et al. Human stanniocalcin: a possible hormonal regulator of mineral metabolism. Proc Natl Acad Sci U S A. 1996; 93:1792.
490. Orlando RA, Takeda T, Zak B, et al. The glomerular epithelial cell antiadhesin podocalyxin associates with the actin cytoskeleton through interactions with ezrin. J Am Soc Nephrol. 2001;12:1589.
491. Orwoll ES. The milk-alkali syndrome: Current concepts. Ann Intern Med. 1982;97:242.
http://www.ncbi.nlm.nih.gov/pubmed/7049033

492. Pabico RC, McKenna BA. Metabolic problems in renal transplant patients. Persistent hyperparathyroidism and hypophosphatemia: effects of intravenous calcium infusion. Transplant Proc. 1988;20:438.
http://www.ncbi.nlm.nih.gov/pubmed/3279634
493. Pallais JC, Kifor O, Chen YB, et al. Acquired hypocalciuric hypercalce-mia due to autoantibodies against the calcium-sensing receptor. N Engl J Med. 2004;351:362.
http://www.ncbi.nlm.nih.gov/pubmed/15269316
494. Palmer LG, Frindt G. Amiloride-sensitive Na channels from the apical membrane of the rat cortical collecting tubule. Proc Natl Acad Sci U S A. 1986; 83:2767.
495. Palmer PE. Tumoural calcinosis. Br J Radiol. 1966;39:518.
http://www.ncbi.nlm.nih.gov/pubmed/5941999
496. Panda DK, Miao D, Bolivar I, et al. Inactivation of the 25-hydroxyvitamin D 1α-hydroxylase and vitamin D receptor demonstrates independent and interdependent effects of calcium and vitamin D on skeletal and mineral homeostasis. J Biol Chem. 2004;279:16754.
http://www.ncbi.nlm.nih.gov/pubmed/14739296
497. Parfitt AM. The interactions of thiazide diuretics with parathyroid hormone and vitamin D: Studies in patients with hypoparathyroidism. J Clin Invest. 1972;51:1879.
498. Parfitt AM. The spectrum of hypoparathyroidism. J Clin Endocrinol Metab. 1972;34:152.
http://www.ncbi.nlm.nih.gov/pubmed/4621463
499. Parfitt AM. The hyperparathyroidism of chronic renal failure: a disorder of growth. Kidney Int. 1997;52:3.
http://www.ncbi.nlm.nih.gov/pubmed/9211340
500. Parfitt AM, Kleerekoper M, Cruz C. Reduced phosphate reabsorption unrelated to parathyroid hormone after renal transplantation: implications for the pathogenesis of hyperparathyroidism in chronic renal failure. Miner Electrolyte Metab. 1986;12:356.
http://www.ncbi.nlm.nih.gov/pubmed/3543637
501. Parker MS, Klein I, Haussler MR, et al. Tumor-induced osteomalacia: Evidence of a surgically correctable alteration in vitamin D metabolism. JAMA. 1981;245:492.
http://www.ncbi.nlm.nih.gov/pubmed/7452873
502. Pastoriza-Munoz E, Colindres RE, Lassiter WE, et al. Effect of parathyroid hormone on phosphate reabsorption in rat distal convolution. Am J Physiol. 1978;235:F321–F330.
503. Patrie KM, Drescher AJ, Goyal M, et al. The membrane-associated guanylate kinase protein MAGI-1 binds megalin and is present in glomerular podocytes. J Am Soc Nephrol. 2001;12:667.
http://www.ncbi.nlm.nih.gov/pubmed/11274227
504. Patrie KM, Drescher AJ, Welihinda A, et al. Interaction of two actin-binding proteins, synaptopodin and alpha-actinin-4, with the tight junction protein MAGI-1. J Biol Chem. 2002;277:30183.
505. Patten JL, Levine MA. Immunochemical analysis of the α-subunit of the stimulatory G-protein of adenylyl cyclase in patients with Albright's hereditary osteodystrophy. J Clin Endocrinol Metab. 1990;71:1208.
506. Peacock M, Bilezikian JP, Klassen PS, et al. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. J Clin Endo Metab. 2005;90:135.
507. Pearce SHS, Brown EM. Calcium-sensing receptor mutations: insights into a structurally and functionally novel receptor. J Clin Endo Metab. 1996;81:1309.
http://www.ncbi.nlm.nih.gov/pubmed/8636322
508. Peraino RA, Suki WN. Phosphate transport by isolated rabbit cortical collecting tubule. Am J Physiol. 1980;238:F358–F362.
509. Pitts RF, Alexander RS. The renal reabsorptive mechanism for inorganic phosphate in normal and acidotic dogs. Am J Physiol. 1944;142:648.
510. Pizurki L, Rizzoli R, Caverzasio J, et al. Effect of transforming growth factor-alpha and parathyroid hormone-related protein on phosphate transport in renal cells. Am J Physiol. 1990;259:929.
http://www.ncbi.nlm.nih.gov/pubmed/2175562
511. Pollak MR, Brown EM, Chou YH, et al. Mutations in the human Ca2+-sensing receptor gene cause familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. Cell. 1993;75:1297.
512. Pollak MR, Brown EM, Chou YH, et al. Mutations in the human Ca^{2+}-sensing receptor gene cause familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. Cell. 1993;75:1297.
513. Pollak MR, Brown EM, Estep HL, et al. Autosomal dominant hypocalcaemia caused by a Ca^{2+} -sensing receptor gene mutation. Nat Genet. 1994;8:303.
http://www.ncbi.nlm.nih.gov/pubmed/7874174
514. Popovtzer MM, Subryan VL, Alfrey AC. The acute effect of chlorothiazide on serum ionized calcium: Evidence for a parathyroid hormone-dependent mechanism. J Clin Invest. 1975;55:1295.
http://www.ncbi.nlm.nih.gov/pubmed/1133175
515. Poulos PP. The renal tubular reabsorption and urinary excretion of calcium by the dog. J Lab Clin Med. 1957;49:253.
http://www.ncbi.nlm.nih.gov/pubmed/13398690
516. Pribanic S, Gisler SM, Bacic D, et al. Interactions of MAP17 with the NaPi-IIa/PDZK1 protein complex in renal proximal tubular cells. Am J Physiol Renal Physiol. 2003;285:784.
517. Pribanic S, Loffing J, Madjdpour C, et al. Expression of visinin-like protein-3 in mouse kidney. Nephron Physiol. 2003;95:76.
http://www.ncbi.nlm.nih.gov/pubmed/14694264
518. Prie D, Beck L, Friedlander G, et al. Sodium-phosphate cotransporters, nephrolithiasis and bone demineralization. Curr Opin Nephrol Hypertens. 2004;13:675.
http://www.ncbi.nlm.nih.gov/pubmed/15483460
519. Prie D, Beck L, Silve C, et al. Hypophosphatemia and calcium nephrolithiasis. Nephron Exper Nephrol. 2004;98:50.
520. Prie D, Huart V, Bakouh N, et al. Nephrolithiasis and osteoporosis associated with hypophosphatemia caused by mutations in the type 2a sodium-phosphate cotransporter. N Engl J Med. 2002;347:983.
http://www.ncbi.nlm.nih.gov/pubmed/12324554
521. Prince MJ, Schaeffer PC, Goldsmith RS, et al. Hyperphosphatemic tumoral calcinosis: association with elevation of serum 1,25-dihydroxycholecalciferol concentrations. Ann Intern Med. 1982;96:586.
522. Prins JG, Schrijver H, Staghouwer JM. Hyperalimentation, hypophosphatemia and coma. Lancet. 1973;1:1253.
http://www.ncbi.nlm.nih.gov/pubmed/4122603
523. Pritchard JA. The use of magnesium ion in the management of eclamptogenic toxemias. Surg Gynecol Obstet. 1955;100:131.
http://www.ncbi.nlm.nih.gov/pubmed/13238166
524. Pruyne D, Evangelista M, Yang C, et al. Role of formins in actin assembly: nucleation and barbed-end association. Science. 2002;297:612.
http://www.ncbi.nlm.nih.gov/pubmed/12052901
525. Pullman TN, Lavender AR, Aho I, et al. Direct renal action of a purified parathyroid extract. Endocrinology. 1960;67:570.
http://www.ncbi.nlm.nih.gov/pubmed/13738473
526. Puschett JB, Goldberg M. The relationship between the renal handling of phosphate and bicarbonate in man. J Lab Clin Med. 1969;73:956.
http://www.ncbi.nlm.nih.gov/pubmed/5786461
527. Quamme GA. Effect of calcitonin and magnesium transport in the rat nephron. Am J Physiol. 1980;238:573.
http://www.ncbi.nlm.nih.gov/pubmed/7386624
528. Quamme GA. Influence of volume expansion on Mg influx into the superficial proximal tubule. Kidney Int. 1980;17:721A.
529. Quamme GA. Effect of hypercalcemia on renal tubular handling of calcium and magnesium. Canadian J Physiol Pharmacol. 1982;60:1275.
530. Quamme GA. Urinary alkalinization may not result in an increase in urinary phosphate excretion. Kidney Int. 1984;25:150.
531. Quamme GA. Renal magnesium handling: new insights in understanding old problems. Kidney Int. 1997;52:1180.
http://www.ncbi.nlm.nih.gov/pubmed/9350641
532. Quamme GA, Carney SC, Wong NLM. Effect of parathyroid hormone on renal calcium and magnesium reabsorption in magnesium deficient rats. Pflugers Arch. 1980;58:1.
http://www.ncbi.nlm.nih.gov/pubmed/7191964
533. Quamme GA, De Rouffignac C. Renal magnesium handling. In: Selding D, Giebisch G, eds. The Kidney. Lippincott Williams and Williams; 2004:1711.
534. Quamme GA, Dirks JH. Intraluminal and contraluminal magnesium on magnesium and calcium transfer in the rat nephron. Am J Physiol. 1980;238:F187–F198.
535. Quamme GA, Mizgala CL, Wong NLM, et al. Effects of intraluminal pH and dietary phosphate on phosphate transport in the proximal convoluted tubule. Am J Physiol. 1985;249:F759–F768.
536. Quarles LD. Evidence for a bone-kidney axis regulating phosphate homeostasis. J Clin Invest. 2003;112:642.
http://www.ncbi.nlm.nih.gov/pubmed/12952909
537. Quarles LD. FGF23, PHEX, and MEPE regulation of phosphate homeostasis and skeletal mineralization. Am J Physiol Endocrinol Metab. 2003;285:1.
538. Raanani P, Berkowicz M, Harden I, et al. Severe hypophosphataemia in auto-graft recipients during accelerated leucocyte recovery. Br J Haematol. 1995;91:1031.
539. Raggi P, Boulay A, Chasan-Taber S, et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol. 2002;39:695.
540. Raghuram V, Mak DD, Foskett JK. Regulation of cystic fibrosis transmembrane conductance regulator single-channel gating by bivalent PDZ-domain-mediated interaction. Proc Natl Acad Sci U S A. 2001;98:1300.

541. Ramachandran C, Brunette MG. Renal Na/Ca^{2+} exchange system is located exclusively in the distal tubule. Biochem J. 1989;257:259.
http://www.ncbi.nlm.nih.gov/pubmed/2920016
542. Randall RE Jr, Chen MD, Spray CC. Hypermagnesemia in renal failure. Ann Intern Med. 1949;61:73.
543. Rasmussen H, Fontaine O, Max EE, et al. Effect of 1alpha-hydroxy-vitamin D_3 administration on calcium transport in chick intestine brush border membrane vesicles. J Biol Chem. 1979;254:2993.
http://www.ncbi.nlm.nih.gov/pubmed/429331
544. Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. Endocrine Rev. 1993;14:348.
545. Reilly RF, Shugrue CA. cDNA cloning of a renal Na^+/Ca^{2+} exchanger. Am J Physiol. 1992;262:F1105–F1109.
546. Ribeiro CP, Mandel LJ. Parathyroid hormone inhibits proximal tubule. Am J Physiol. 1992;262:F209–F216.
547. Ribeiro S, Ramos A, Brandao A, et al. Cardiac valve calcification in haemodialysis patients: role of calcium-phosphate metabolism. Nephrol Dial Transplant. 1998;13:2037.
548. Riccardi D, Park J, Lee WS, et al. Cloning and functional expression of a rat kidney extracellular calcium/polyvalent cation-sensing receptor. Proc Natl Acad Sci U S A. 1995;92:131.
http://www.ncbi.nlm.nih.gov/pubmed/7816802
549. Riedler GF, Scheitlin WA. Hypophosphatemia in septicemia: Higher incidence in gram-negative than in gram-positive infections. Br Med J. 1969;1:753.
http://www.ncbi.nlm.nih.gov/pubmed/4890205
550. Riminucci M, Collins MT, Fedarko NS, et al. FGF-23 in fibrous dysplasia of bone and its relationship to renal phosphate wasting. J Clin Invest. 2003;112:683.
http://www.ncbi.nlm.nih.gov/pubmed/12952917
551. Riminucci M, Fisher LW, Shenker A, et al. Fibrous dysplasia of bone in the McCune-Albright syndrome: abnormalities in bone formation. Am J Pathol. 1997;151:1587.
552. Rocha AS, Magaldi JB, Kokko JP. Calcium and phosphate transport in isolated segments of rabbit Henle's loop. J Clin Invest. 1977;59:975.
http://www.ncbi.nlm.nih.gov/pubmed/856875
553. Rodriguez HJ, Villareal H, Klahr S. Pseudohypoparathyroidism type II: Restoration of normal renal responsiveness to parathyroid hormone by calcium administration. J Clin Endocrinol Metab. 1974;39:693.
http://www.ncbi.nlm.nih.gov/pubmed/4370302
554. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind comparative trial. Cancer J. 2001;7:377.
http://www.ncbi.nlm.nih.gov/pubmed/11693896
555. Rosenbaum RW, Hruska KA, Korkor A, et al. Decreased phosphate reabsorption after renal transplantation: Evidence for a mechanism independent of calcium and parathyroid hormone. Kidney Int. 1981;19:568.
http://www.ncbi.nlm.nih.gov/pubmed/6264200
556. Rosenbaum RW, Hruska KA, Korkor A, et al. Decreased phosphate reabsorption after renal transplantation: Evidence for a mechanism independent of calcium and parathyroid hormone. Kidney Int. 1981;19:568.
http://www.ncbi.nlm.nih.gov/pubmed/6264200
557. Rosental R, Babarykin D, Fomina O, et al. Hypophosphatemia after successful transplantation of the kidney. Clinico-experimental study. Z Urol Nephrol. 1982;75:393.
http://www.ncbi.nlm.nih.gov/pubmed/6750972
558. Rostand SG, Sanders C, Kirk KA, et al. Myocardial calcification and cardiac dysfunction in chronic renal failure. Am J Med. 1988;85:651.
http://www.ncbi.nlm.nih.gov/pubmed/3055977
559. Roth KS, Foreman JW, Segal S. The Fanconi syndrome and mechanisms of tubular dysfunction. Kidney Int. 1981;20:705.
http://www.ncbi.nlm.nih.gov/pubmed/7334745
560. Rouse D, Ng RCK, Suki WN. Calcium transport in the pars recta and thin descending limb of Henle of the rabbit, perfused in vitro. J Clin Invest. 1980;65:37.
http://www.ncbi.nlm.nih.gov/pubmed/6243139
561. Rowe PS. The wrickkened pathways of FGF23, MEPE and PHEX. Crit Rev Oral Biol Med. 2004;15:264.
http://www.ncbi.nlm.nih.gov/pubmed/15470265
562. Rowe PS, de Zoysa PA, Dong R, et al. MEPE, a new gene expressed in bone marrow and tumors causing osteomalacia. Genomics. 2000;67:54.
http://www.ncbi.nlm.nih.gov/pubmed/10945470
563. Rowe PS, Garrett IR, Schwarz PM, et al. Surface plasmon resonance (SPR) confirms that MEPE binds to PHEX via the MEPE-ASARM motif: a model for impaired mineralization in X-linked rickets (HYP). Bone. 2005;36:33.
http://www.ncbi.nlm.nih.gov/pubmed/15664000
564. Rowe PS, Kumagai Y, Gutierrez G, et al. MEPE has the properties of an osteoblastic phosphatonin and minhibin. Bone. 2004;34:303.
http://www.ncbi.nlm.nih.gov/pubmed/14962809
565. Rowe PSN, Ong ACM, Cockerill FJ, et al. Candidate 56 and 58 kDa protein(s) responsible for mediating the renal defects in oncogenic hypophosphatemic osteomalacia. Bone. 1996;18:159.
http://www.ncbi.nlm.nih.gov/pubmed/8833210
566. Rude RK. Magnesium deficiency in parathyroid function. In: Bilezikian JP, Marcus R, Levine MA, eds. The Parathyroids: Basic and Clinical Concepts. San Diego: Academic Press; 2001:763.
567. Rude RK, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone organ resistance in human magnesium deficiency. Clin Endocrinol. 1976;5:209.
http://www.ncbi.nlm.nih.gov/pubmed/182417
568. Rutherford E, Mercado A, Hruska K, et al. An evaluation of a new and effective phosphate binding agent. Trans Am Soc Artif Intern Organs. 1973;19:446.
http://www.ncbi.nlm.nih.gov/pubmed/4722760
569. Ryan WG, Nibbe AF, Schwartz TB, et al. Fibrous dysplasia of bone with vitamin D resistant rickets: a case study. Metabolism. 1968;17:988.
http://www.ncbi.nlm.nih.gov/pubmed/5724172
570. Ryback RS, Eckardt MJ, Pautler CP. Clinical relationships between serum phosphorus and other blood chemistry values in alcoholics. Arch Intern Med. 1980;140:673.
http://www.ncbi.nlm.nih.gov/pubmed/7396592
571. Sacktor B. Transport in membrane vesicles isolated from the Mammalian kidney and intestine. In: Sanadi R, ed. Current Topics in Bioenergetics. New York: Academic Press; 1977:30.
572. Saito H, Kusano K, Kinosaki M, et al. Human fibroblast growth factor-23 mutants suppress Na+ -dependent phosphate co-transport activity and 1alpha,25-dihydroxyvitamin D3 production. J Biol Chem. 2003;278:2206.
http://www.ncbi.nlm.nih.gov/pubmed/12419819
573. Sakamoto A, Liu J, Greene A, et al. Tissue-specific imprinting of the G protein Gs{alpha} is associated with tissue-specific differences in histone methylation. Hum Mol Genet. 2004;1913:819.
http://www.ncbi.nlm.nih.gov/pubmed/14976161
574. Sakhaee K, Brinker K, Helderman JH, et al. Disturbances in mineral metabolism after successful renal transplantation. Miner Electrolyte Metab. 1985;11:167.
http://www.ncbi.nlm.nih.gov/pubmed/3892264
575. Salander H, Tisell LE. Incidence of hypoparathyroidism after radical surgery for thyroid carcinoma and autotransplantation of parathyroid glands. Am J Surg. 1977;134:358.
http://www.ncbi.nlm.nih.gov/pubmed/900338
576. Saunders Y, Ross JR, Broadley KE, et al. Systematic review of bisphosphonates for hypercalcaemia of malignancy. Palliat Med. 2004;18:418.
http://www.ncbi.nlm.nih.gov/pubmed/15332420
577. Schatzmann HJ. The red cell calcium pump. Ann Rev Physiol. 1983;45:303.
http://www.ncbi.nlm.nih.gov/pubmed/6342519
578. Scheinman SJ. X-linked hypercalciuric nephrolithiasis: Clinical syndromes and chloride channel mutations. Kidney Int. 1998;53:3.
http://www.ncbi.nlm.nih.gov/pubmed/9452994
579. Schiavi SC, Kumar R. The phosphatonin pathway: New insights in phosphate homeostasis. Kidney Int. 2004;65:1.
http://www.ncbi.nlm.nih.gov/pubmed/14675031
580. Schilsky RL, Anderson T. Hypomagnesemia and renal magnesium wasting in patients receiving cisplatin. Ann Intern Med. 1979;90:926.
http://www.ncbi.nlm.nih.gov/pubmed/375794
581. Schneider AB, Sherwood LM. Pathogenesis and management of hypoparathyroidism and hypocalcemic disorders. Metabolism. 1975;24:871.
http://www.ncbi.nlm.nih.gov/pubmed/166271
582. Schwab SJ, Hammerman MR. Mechanisms of phosphate exit across the basolateral membrane of the renal proximal tubule cell. Clin Res. 1984;32:530.
583. Scoble J, Mills S, Hruska KA. Calcium transport (Ca^{2+}) in renal basolateral vesicles (BLMV): Effects of parathyroid hormone (PTH). J Clin Invest. 1985;75:1096.
584. Segawa H, Kaneko I, Takahashi A, et al. Growth-related renal type II Na/Pi cotransporter. J Biol Chem. 2002;277:19665.
http://www.ncbi.nlm.nih.gov/pubmed/11880379
585. Segawa H, Kaneko I, Yamanaka S, et al. Intestinal Na-P(i) cotransporter adaptation to dietary P(i) content in vitamin D receptor null mice. Am J Physiol Renal Physiol. 2004;287:39.
http://www.ncbi.nlm.nih.gov/pubmed/14996670
586. Segawa H, Kawakami E, Kaneko I, et al. Effect of hydrolysis-resistant FGF23-R179Q on dietary phosphate regulation of the renal type-II Na/Pi transporter. Pfugers Arch. 2003;446:585.
http://www.ncbi.nlm.nih.gov/pubmed/12851820

587. Seldin DW, Tarail R. The metabolism of glucose and electrolytes in diabetic acidosis. J Clin Invest. 1950;29:552.
http://www.ncbi.nlm.nih.gov/pubmed/15415460
588. Seller RH, Cangiano J, Kim EE. Digitalis toxicity and hypomagnesemia. Am Heart J. 1970;79:57.
http://www.ncbi.nlm.nih.gov/pubmed/5410283
589. Seyberth HW, Segre GV, Hamet P. Characterization of the group of patients with hypercalcemia of cancer who respond to treatment with prostaglandin synthesis inhibitors. Trans Assoc Am Physicians. 1976;89:92.
http://www.ncbi.nlm.nih.gov/pubmed/190750
590. Shanahan CM, Cary NRB, Metcalfe JC, et al. High expression of genes for calcification-regulating proteins in human atherosclerotic plaques. J Clin Invest. 1994;93:2393.
http://www.ncbi.nlm.nih.gov/pubmed/8200973
591. Shareghi GR, Agus ZS. Magnesium transport in the cortical thick ascending limb of Henle's loop of the rabbit. J Clin Invest. 1982;69:759.
http://www.ncbi.nlm.nih.gov/pubmed/7076846
592. Shareghi GR, Agus ZS. Phosphate transport in the light segment of the rabbit cortical collecting tubule. Am J Physiol. 1982;242:F379–F384.
593. Shareghi GR, Stoner LC. Calcium transport across segments of the rabbit distal nephron in vitro. Am J Physiol. 1978;235:F367.
594. Shenolikar S, Voltz JW, Cunningham R, et al. Regulation of ion transport by the NHERF family of PDZ proteins. Physiology (Bethesda). 2004;19:362.
http://www.ncbi.nlm.nih.gov/pubmed/15546854
595. Shenolikar S, Voltz JW, Minkoff CM, et al. Targeted disruption of the mouse NHERF-1 gene promotes internalization of proximal tubule sodium-phosphate cotransporter type IIa and renal phosphate wasting. Proc Natl Acad Sci U S A. 2002; 99:11470.
http://www.ncbi.nlm.nih.gov/pubmed/12169661
596. Shenolikar S, Weinman EJ. NHERF: targeting and trafficking membrane proteins. Am J Physiol Renal Physiol. 2001;280:389.
http://www.ncbi.nlm.nih.gov/pubmed/11181400
597. Sherwood LM, Santora AC. Hypoparathyroid states in the differential diagnosis of hypocalcemia. In: Bilezikian JP, Marcus R, Levine MA, eds. The Parathyroids: Basic and Clinical Concepts. New York: Raven Press; 1994:747.
598. Shields HM. Rapid fall of serum phosphorus secondary to antacid therapy. Gastroenterology. 1978;75:1137.
599. Shils ME. Experimental human magnesium depletion. Medicine. 1969;48:61.
http://www.ncbi.nlm.nih.gov/pubmed/5763574
600. Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res. 2004; 19:429.
http://www.ncbi.nlm.nih.gov/pubmed/15040831
601. Shimada T, Kakjitani M, Hasegawa H, et al. Targeted ablation of FGF-23 causes hyperphosphatemia. Increased 1,25-dihydroxyvitamin D level and severe growth retardation. J Bone Min Res. 2002;17(1):S168.
602. Shimada T, Mizutani S, Muto T, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci U S A. 2001;98:6500.
http://www.ncbi.nlm.nih.gov/pubmed/11344269
603. Shimada T, Muto T, Urakawa I, et al. Mutant FGF-23 responsible for autosomal dominant hypophosphatemic rickets is resistant to proteolytic cleavage and causes hypophosphatemia in vivo. Endocrinology. 2002;143:3179.
604. Shimada T, Urakawa I, Yamazaki Y, et al. FGF-23 transgenic mice demonstrate hypophosphatemic rickets with reduced expression of sodium phosphate cotransporter type IIa. Biochem Biophys Res Commun. 2004;314:409.
605. Shimizu T, Nakamura M, Yoshitomi K. Interaction of trichlormethiazide or amiloride with PTH in stimulating calcium absorption in the rabbit connecting tubule. Am J Physiol. 1991;261:F36.
606. Shimizu T, Yoshitomi K, Nakamura M. Effect of parathyroid hormone on the connecting tubule from the rabbit kidney: Biphasic response of transmural voltage. Pfugers Arch. 1990;416:257.
http://www.ncbi.nlm.nih.gov/pubmed/2381763
607. Shimizu T, Yoshitomi K, Nakamura M, et.al. Effects of PTH, calcitonin, and cAMP on calcium transport in rabbit distal nephron segments. Am J Physiol. 1990;259:F408–F414.
608. Shirley DG, Pooujeol P, LeGrimellec C. Phosphate, calcium and magnesium fuxes into the lumen of the rat proximal convoluted tubule. Pfugers Arch. 1976;362:247.
http://www.ncbi.nlm.nih.gov/pubmed/944432
609. Shirley DG, Faria NJR, Unwin RJ, et al. Direct micropuncture evidence that matrix extracellular phosphoglycoprotein inhibits proximal tubular phosphate reabsorption. Nephrol Dial Transplant. 2010;25:3191.
610. Silver J, Neale G, Thompson GR. Effect of phenobarbitone treatment on vitamin D metabolism in mammals. Clin Sci Mol Med. 1974;46:433.
http://www.ncbi.nlm.nih.gov/pubmed/4364312
611. Silver J, Sela SB, Naveh-Man T. Regulation of parathyroid cell proliferation. Curr Opin Nephrol Hypertens. 1997;6:321.
http://www.ncbi.nlm.nih.gov/pubmed/9263680
612. Silvis SE, DiBartolomeo AG, Aaker HM. Hypophosphatemia and neurologic changes secondary to oral caloric intake: A variant of hyperalimentation syndrome. Am J Gastroenterol. 1980;73:215.
http://www.ncbi.nlm.nih.gov/pubmed/6773412
613. Simon DB, Lu Y, Chaote KA, et al. Paracellin-I, a renal tight junction protein required for paracellular Mg^{2+} resorption. Science. 1999;285:103.
http://www.ncbi.nlm.nih.gov/pubmed/10390358
614. Simon DB, Nelson-Williams C, Bia MJ, et al. Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. Nat Genet. 1996;12:24.
http://www.ncbi.nlm.nih.gov/pubmed/8528245
615. Singer FR, Neer RM, Murray JM. Mithramycin treatment of intractable hypercalcemia due to parathyroid adenomas. N Engl J Med. 1970;283:634.
http://www.ncbi.nlm.nih.gov/pubmed/5450637
616. Singer FR, Ritch PS, Lad TE. Treatment of hypercalcemia of malignancy with intravenous etidronate. Arch Intern Med. 1991;151:471.
http://www.ncbi.nlm.nih.gov/pubmed/1900410
617. Singer FR, Sharp CF, Rude RK. Pathogenesis of hypercalcemia in malignancy. Miner Electrolyte Metab. 1979;2:161.
618. Siris ES, Sherman WH, Baguiran DC. Effects of dichloromethylene-diphos-phonate on skeletal mobilization of calcium in multiple myeloma. N Engl J Med. 1980;302:310.
http://www.ncbi.nlm.nih.gov/pubmed/6444241
619. Sitara D, Razzaque MS, Hesse M, et al. Homozygous ablation of fibroblast growth factor-23 results in hyperphosphatemia and impaired skeletogenesis, and reverses hypophosphatemia in Phex-deficient mice. Matrix Biol. 2004; 23:421.
http://www.ncbi.nlm.nih.gov/pubmed/15579309
620. Slatopolsky E. Pathophysiology of calcium, magnesium and phosphorus. In: Klahr S, ed. The Kidney and Body Fluids in Health and Disease. New York: Plenum Press; 1984:269.
621. Slatopolsky E, Burke SK, Dillon MA. RenaGel, a nonabsorbed calcium and aluminum-free phosphate-binder, lowers serum phosphorus and parathyroid hormone. Kidney Int. 1999;55:299.
http://www.ncbi.nlm.nih.gov/pubmed/9893140
622. Slatopolsky E, Caglar S, Gradowska L, et al. On the prevention of secondary hyperparathyroidism in experimental chronic renal disease using "proportional reduction" of dietary phosphorus intake. Kidney Int. 1972;2:147.
http://www.ncbi.nlm.nih.gov/pubmed/4669450
623. Slatopolsky E, Finch J, Denda M, et al. Phosphorus restriction prevents parathyroid gland growth. High phosphorus directly stimulates PTH secretion in vitro. J Clin Invest. 1996;97:2534.
http://www.ncbi.nlm.nih.gov/pubmed/8647946
624. Slatopolsky E, Gradowska L, Kashemsant C. The control of phosphate excretion in uremia. J Clin Invest. 1966;45:672.
625. Slatopolsky E, Robson AM, Elkan I, et al. Control of phosphate excretion in uremic man. J Clin Invest. 1968;47:1865–1874.
http://www.ncbi.nlm.nih.gov/pubmed/5666116
626. Slatopolsky E, Weerts C, Lopez-Hilker S, et al. Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. N Engl J Med. 1986;315:157.
http://www.ncbi.nlm.nih.gov/pubmed/3724805
627. Slatopolsky E, Weerts C, Norwood K, et al. Long-term effects of calcium carbonate and 2.5 mEq/liter calcium dialysate on mineral metabolism. Kidney Int. 1989;36:897.
http://www.ncbi.nlm.nih.gov/pubmed/2615197
628. Slatopolsky E, Weerts C, Thielan J. Marked suppression of secondary hyperparathyroidism by intravenous administration of 1,25-dihydroxycholecalciferol in uremic patients. J Clin Invest. 1984;74:2136.
629. Slavin RE, Wen J, Kumar D, et al. Familial tumoral calcinosis. A clinical, histopathologic, and ultrastructural study with an analysis of its calcifying process and pathogenesis. Am J Surg Pathol. 1993;17:788.
http://www.ncbi.nlm.nih.gov/pubmed/8338191
630. Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: The USRDS waves 1, 3, and 4 Study. J Am Soc Nephrol. 2005;16:1788–1793.
http://www.ncbi.nlm.nih.gov/pubmed/15814832
631. Smith EL, Gilligan C. Exercise and bone mass. In: DeLuca HF, Mazess R, eds. Osteoporosis: Physiological Basis, Assessment and Treatment. New York: Elsevier Science Publishing; 1990:285.
632. Smith EP, Boyd J, Frank GR, et al. Estrogen resistance caused by a mutation in the estrogen receptor gene in a man. N Engl J Med. 1994;331:1088.
http://www.ncbi.nlm.nih.gov/pubmed/8090165

633. Smith WJ, Nassar N, Bretscher A, et al. Structure of the active N-terminal domain of Ezrin. Conformational and mobility changes identify keystone interactions. J Biol Chem. 2003;278:4949.
http://www.ncbi.nlm.nih.gov/pubmed/12429733
634. Sneddon WB, Magyar CE, Willick GE, et al. Ligand-selective dissociation of activation and internalization of the parathyroid hormone (PTH) receptor: conditional efficacy of PTH peptide fragments. Endocrinology. 2004;145:2815.
http://www.ncbi.nlm.nih.gov/pubmed/15016722
635. Sorribas V, Lotscher M, Loffing J, et al. Cellular mechanisms of the age-related decrease in renal phosphate reabsorption. Kidney Int. 1996;50:855.
http://www.ncbi.nlm.nih.gov/pubmed/8872960
636. Sorribas V, Markovich D, Hayes G, et al. Cloning of a Na/Pi cotransporter from opossum kidney cells. J Biol Chem. 1994;269:6615.
http://www.ncbi.nlm.nih.gov/pubmed/7509808
637. Sorribas V, Markovich D, Verri T, et al. Thyroid hormone stimulation of Na/ Pi-cotransport in opossum kidney cells. Pfugers Arch. 1995;431:266.
http://www.ncbi.nlm.nih.gov/pubmed/9026788
638. Stauber A, Radanovic T, Stange G, et al. Regulation of intestinal phosphate transport. II. Metabolic acidosis stimulates Na(+)-dependent phosphate absorption and expression of the Na(+)-P(i) cotransporter NaPi-IIb in small intestine. Am J Physiol. Gastrointest Liver Physiol. 2005;288:501.
http://www.ncbi.nlm.nih.gov/pubmed/15701624
639. Stauffer TP, Guerini D, Carafoli E. Tissue distribution of the four gene products of the plasma membrane Ca^{2+} pump - a study using specific antibodies. J Biol Chem. 1995;270:12184.
http://www.ncbi.nlm.nih.gov/pubmed/7538133
640. Steele TH, Stromberg BA, Larmore CA. Renal resistance to parathyroid hormone during phosphorus deprivation. J Clin Invest. 1976;58:1461.
http://www.ncbi.nlm.nih.gov/pubmed/186491
641. Steele TH, Weng SF, Evenson MA. The contributions of the chronically diseased kidney to magnesium homeostasis in man. J Lab Clin Med. 1968; 71:455.
http://www.ncbi.nlm.nih.gov/pubmed/5650925
642. Stein GS, Lian JB. Molecular mechanisms mediating proliferation/differentiation interrelationships during progressive development of the osteoblast phenotype. Endocrine Rev 1993;14:424.
643. Steiner RW, Ziegler M, Halasz NA, et al. Effect of daily oral vitamin D and calcium therapy, hypophosphatemia, and endogenous 1–25 dihydroxycholecalciferol on parathyroid hormone and phosphate wasting in renal transplant recipients. Transplantation. 1993;56:843.
http://www.ncbi.nlm.nih.gov/pubmed/8212205
644. Stewart AF. Hypercalcemia associated with cancer. N Eng J Med. 2005; 352:373.
http://www.ncbi.nlm.nih.gov/pubmed/15673803
645. Stock JL, Marcus R. eds. Medical management of primary hyperparathyroidism. In: Bilezik JP, Marcus R, Levine MA, eds. The Parathyroids: Basic and Clinical Concepts. New York: Raven Press; 1994:519.
646. Stoeckle JD, Hardy HL, Weber AL. Chronic beryllium disease: Long-term follow up of sixty cases and selective review of the literature. Am J Med. 1969;46:545.
http://www.ncbi.nlm.nih.gov/pubmed/4892951
647. Stoll R, Kinne R, Murer H, et al. Phosphate transport by rat renal brush border membrane vesicles: Influence of dietary phosphate, thyroparathyroidectomy, and 1,25-dihydroxyvitamin D_3. Pfugers Arch. 1979;380:47.
http://www.ncbi.nlm.nih.gov/pubmed/572037
648. Strewler GJ. FGF23, hypophosphatemia, and rickets: has phosphatonin been found? Proc Natl Acad Sci U S A. 2001;98:5945.
http://www.ncbi.nlm.nih.gov/pubmed/11371627
649. Suh SM, Tashjian AH, Matsuo N. Pathogenesis of hypocalcemia in primary hypomagnesemia: Normal end-organ responsiveness to parathyroid hormone, impaired parathyroid gland function. J Clin Invest. 1973;52:153.
http://www.ncbi.nlm.nih.gov/pubmed/4345201
650. Suki WN, Eknoyan G, Rector FC. The renal diluting and concentrating mechanisms in hypercalcemia. Nephron. 1969;6:50.
http://www.ncbi.nlm.nih.gov/pubmed/5772764
651. Suki WN, Rouse D, Ng RCK, et al. Calcium transport in the thick ascending limb of Henle: Heterogeneity of function in the medullary and cortical segments. J Clin Invest. 1980;68:1004.
652. Sutton RAL, Wong NLM, Dirks JH. Effects of metabolic acidosis and alkalosis on sodium transport in the dog kidney. Kidney Int. 1979;15:520.
http://www.ncbi.nlm.nih.gov/pubmed/480784
653. Swiatecka-Urban A, Duhaime M, Coutermarsh B, et al. PDZ domain interaction controls the endocytic recycling of the cystic fibrosis transmembrane conductance regulator. J Biol Chem. 2002;277:40099.
http://www.ncbi.nlm.nih.gov/pubmed/12167629
654. Takahashi Y, Tanaka A, Nakamura T, et al. Nicotinamide suppresses hyperphosphatemia in hemodialysis patients. Kidney Int. 2004;65:1099.
655. Takeda T, McQuistan T, Orlando RA, et al. Loss of glomerular foot processes is associated with uncoupling of podocalyxin from the actin cytoskeleton. J Clin Invest. 2001;108:289.
http://www.ncbi.nlm.nih.gov/pubmed/11457882
656. Takeuchi Y, Suzuki H, Ogura S, et al. Venous sampling for fibroblast growth factor-23 confirms preoperative diagnosis of tumor-induced osteomalacia. J Clin Endocrinol Metab. 2004;89:3979.
657. Taylor AN, Wasserman RH. Immunofuorescent localization of vitamin D-dependent calcium-binding proteins. J Histochem Cytochem. 1970;18:107.
http://www.ncbi.nlm.nih.gov/pubmed/4313404
658. Tencza AL, Ichikawa S, Dang A, et al. Hypophosphatemic rickets with hypercalciuria due to mutation in SLC34A3/type IIc sodium-phosphate cotransporter: presentation as hypercalciuria and nephrolithiasis. J Clin Endocri-nol Metab. 2009;94:4433.
http://www.ncbi.nlm.nih.gov/pubmed/19820004
659. Tenenhouse HS. Regulation of phosphorus homeostasis by the type IIa Na/phosphate cotransporter. Annu Rev Nutr. 2005;25:10.1–10.18.
http://www.ncbi.nlm.nih.gov/pubmed/16011465
660. Tenenhouse HS, Martel J, Gauthier C, et al. Differential effects of Npt2a gene ablation and X-linked Hyp mutation on renal expression of Npt2c. Am J Physiol Renal Physiol. 2003;285:1271.
http://www.ncbi.nlm.nih.gov/pubmed/12952859
661. Tenenhouse HS, Murer H. Disorders of renal tubular phosphate transport. J Am Soc Nephrol. 2003;14:240.
http://www.ncbi.nlm.nih.gov/pubmed/12506157
662. Tenenhouse HS, Roy S, Martel J, et al. Differential expression, abundance, and regulation of Na+ -phosphate cotransporter genes in murine kidney. Am J Physiol. 1998;275:F527–F534.
663. Tenenhouse HS, Werner A, Biber J, et al. Renal Na^+ -phosphate cotransport in murine X-linked hypophosphatemic rickets: molecular characterization. J Clin Invest. 1994;93:671.
http://www.ncbi.nlm.nih.gov/pubmed/8113402
664. Terada Y, Knepper MA. Thiazide-sensitive NaCl absorption in rat cortical collecting duct. Am J Physiol. 1990;259:F519.
665. Tieder M. Hereditary hypophosphatemic rickets with hypercalciuria. N Engl J Med. 1985;312:611.
http://www.ncbi.nlm.nih.gov/pubmed/2983203
666. Tieder M, Arie R, Bab I, et al. A new kindred with hereditary hypophosphatemic rickets with hypercalciuria: implications for correct diagnosis and treatment. Nephron. 1992;62:176.
http://www.ncbi.nlm.nih.gov/pubmed/1436310
667. Topaz O, Shurman DL, Bergman R, et al. Mutations in GALNT3, encoding a protein involved in O-linked glycosylation, cause familial tumoral calcinosis. Nat Genet. 2004;36:579.
http://www.ncbi.nlm.nih.gov/pubmed/15133511
668. Travis SF, Sugarman HJ, Ruberg RL, et al. Alterations of red-cell glycolytic intermediates and oxygen transport as a consequence of hypophosphatemia in patients receiving intravenous hyperalimentation. N Engl J Med. 1971;285:763.
http://www.ncbi.nlm.nih.gov/pubmed/4998555
669. Tsokos GC, Balow JE, Spiegel RJ, et al. Renal and metabolic complications of undifferentiated and lymphoblastic lymphomas. Medicine 1981;60:218.
http://www.ncbi.nlm.nih.gov/pubmed/6894477
670. Turner CH, Forwood MR. What role does the osteocyte network play in bone adaptation? Bone. 1995;16:283.
http://www.ncbi.nlm.nih.gov/pubmed/7786630
671. Turner JJO, Stacey JM, Harding B, et al. UROMODULIN mutations cause familial juvenile hyperuricemic nephropathy. J Clin Endocrinol Metab. 2003; 88:1398.
http://www.ncbi.nlm.nih.gov/pubmed/12629136
672. Ullrich KJ, Rumrich G, Kloss S. Active Ca^{2+} reabsorption in the proximal tubule of the rat kidney. Dependence on sodium and buffer transport. Pfugers Arch (Euro J Physiol). 1976;364:223.
http://www.ncbi.nlm.nih.gov/pubmed/986634
673. Urakawa I, Yamazaki Y, Shimada T, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature. 2006;444:770.
http://www.ncbi.nlm.nih.gov/pubmed/17086194
674. van den Heuvel L, Op de Koul K, Knots E, et al. Autosomal recessive hy-pophosphatasemic rickets with hypercalciuria is not caused by mutations in the type II renal sodium/phosphate cotransporter gene. Nephrol Dial Transplant. 2001;16:48.
http://www.ncbi.nlm.nih.gov/pubmed/11568241
675. VanHouten J, Dann P, McGeoch G, et al. The calcium-sensing receptor regulates mammary gland parathyroid hormone-related protein production and calcium transport. J Clin Invest. 2005;113:598.
http://www.ncbi.nlm.nih.gov/pubmed/14966569

676. Verge CF, Lam A, Simpson JM, et al. Effect of therapy in X-linked hypophosphatemic rickets. N Engl J Med. 1991;325:1875.
677. Villa-Bellosta R, Barac-Nieto M, Breusegem SY, et al. Interactions of the growth-related, type IIc renal sodium/phosphate cotransporter with PDZ proteins. Kidney Int. 2007;73:456.
http://www.ncbi.nlm.nih.gov/pubmed/18046316
678. Villa-Bellosta R, Ravera S, Sorribas V, et al. The Na + -Pi cotransporter PiT-2 (SLC20A2) is expressed in the apical membrane of rat renal proximal tubules and regulated by dietary Pi. Am J Physiol Renal Physiol. 2009;296: F691–F699.
679. Virkki LV, Forster IC, Hernando N, et al. Functional characterization of two naturally occurring mutations in the human sodium-phosphate cotransporter type IIa. J Bone Miner Res. 2003;18:2135.
http://www.ncbi.nlm.nih.gov/pubmed/14672348
680. Wagner GF, Vozzolo BL, Jaworski E, et al. Human stanniocalcin inhibits renal phosphate excretion in the rat. J Bone Miner Res. 1997;12:165.
http://www.ncbi.nlm.nih.gov/pubmed/9041047
681. Walker JV, Baran D, Yakub DN. Histoplasmosis with hypercalcemia, renal failure, and papillary necrosis: confusion with sarcoidosis. JAMA. 1977;237:1350.
http://www.ncbi.nlm.nih.gov/pubmed/576482
682. Walls J, Ratcliffe WA, Howell A, et al. Parathyroid hormone and parathyroid-hormone related protein in the investigation of hypercalcemia in two hospital populations. Clin Endocrinol. 1994;41:407.
http://www.ncbi.nlm.nih.gov/pubmed/7955450
683. Walser M. Ion association. VI. Interactions between calcium, magnesium, inorganic phosphate, citrate and protein in normal human plasma. J Clin Invest. 1961;40:723.
http://www.ncbi.nlm.nih.gov/pubmed/13782899
684. Walton RJ, Bijvoet OL. Nomogram for derivation of renal threshold phosphate concentration. Lancet. 1975;2:309.
http://www.ncbi.nlm.nih.gov/pubmed/50513
685. Walton RJ, Russell RG, Smith R. Changes in the renal and extrarenal handling of phosphate induced by disodium etidronate (EHDP) in man. Clin Sci Mol Med. 1975;49:45.
http://www.ncbi.nlm.nih.gov/pubmed/807449
686. Wang S, Yue H, Derin RB, et al. Accessory protein facilitated CFTR-CFTR interaction, a molecular mechanism to potentiate the chloride channel activity. Cell. 2000;103:169.
http://www.ncbi.nlm.nih.gov/pubmed/11051556
687. Ward HN, Pabico RC, McKenna BA, et al. The renal handling of phosphate by renal transplant patients: correlation with serum parathyroid hormone (SPTH), cyclic 3′,5′-adenosine monophosphate (cAMP) urinary excretion, and allograft function. Adv Exp Med Biol. 1977;81:173.
http://www.ncbi.nlm.nih.gov/pubmed/197815
688. Ward LM, Rauch F, White KE, et al. Resolution of severe, adolescent-onset hypophosphatemic rickets following resection of an FGF-23-producing tumour of the distal ulna. Bone. 2004;34:905.
http://www.ncbi.nlm.nih.gov/pubmed/15121023
689. Ward MK, Feest TG, Ellis HA. Osteomalacic dialysis osteodystrophy: Evidence for a water-borne aetiological agent, probably aluminum. Lancet. 1978;1:841.
http://www.ncbi.nlm.nih.gov/pubmed/76795
690. Wasserman RH. Intestinal absorption of calcium and phosphorus. Fed Proc. 1981;40:68.
http://www.ncbi.nlm.nih.gov/pubmed/7192650
691. Wasserman RH. Vitamin D and the dual processes of intestinal calcium absorption. J Nutrition. 2004;134:3137.
http://www.ncbi.nlm.nih.gov/pubmed/15514288
692. Wasserman RH, Corradino RA, Taylor AN. Vitamin D-dependent calcium binding protein: purification and some properties. J Biol Chem. 1968;243:3970.
693. Wasserman RH, Taylor AN. Vitamin D_3-induced calcium binding protein in chick intestinal mucosa. Science 1966;152:791.
http://www.ncbi.nlm.nih.gov/pubmed/17797460
694. Wasserman RH, Taylor AN. Evidence for a vitamin D3-induced calcium-binding protein in new world primates. Proc Soc Exp Biol Med. 1970;136:25.
http://www.ncbi.nlm.nih.gov/pubmed/4322267
695. Watson P, Lazowski D, Han V, et al. Parathyoid hormone restores bone mass and enhances osteoblast insulin-like growth factor I gene expression in ovariectomized rats. Bone. 1995;16:357.
http://www.ncbi.nlm.nih.gov/pubmed/7786639
696. Weinman EJ, Evangelista CM, Steplock D, et al. Essential role for NHERF in cAMP-mediated inhibition of the Na + -HCO3- co-transporter in BSC-1 cells. J Biol Chem. 2001;276:42339.
http://www.ncbi.nlm.nih.gov/pubmed/11535598
697. Weinman EJ, Minkoff C, Shenolikar S. Signal complex regulation of renal transport proteins: NHERF and regulation of NHE3 by PKA. Am J Physiol Renal Physiol. 2000;279:393.
698. Weinman EJ, Steplock D, Donowitz M, et al. NHERF associations with sodium-hydrogen exchanger isoform 3 (NHE3) and ezrin are essential for cAMP-mediated phosphorylation and inhibition of NHE3. Biochemistry. 2000;39:6123.
699. Weinman EJ, Steplock D, Shenolikar S. NHERF-1 uniquely transduces the cAMP signals that inhibit sodium-hydrogen exchange in mouse renal apical membranes. FEBS Lett. 2003;536:141.
http://www.ncbi.nlm.nih.gov/pubmed/12586353
700. Weinman EJ, Steplock D, Wade JB, et al. Ezrin binding domain-deficient NHERF attenuates cAMP-mediated inhibition of Na(+)/H(+) exchange in OK cells. Am J Physiol Renal Physiol. 2001;281:374.
http://www.ncbi.nlm.nih.gov/pubmed/11457730
701. Weinsier RL, Krumdiek CL. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. Am J Clin Nutr. 1981;34:393.
http://www.ncbi.nlm.nih.gov/pubmed/6782855
702. Weinstein LS. Mutations of the Gs alpha-subunit gene in Albright hereditary osteodystrophy detected by denaturing gradient gel electrophoresis. Proc Natl Acad Sci U S A. 1990;87:8287.
http://www.ncbi.nlm.nih.gov/pubmed/2122458
703. Weinstein LS, Liu J, Sakamoto A, et al. Minireview: GNAS: normal and abnormal functions. Endocrinology. 2004;145:5459.
http://www.ncbi.nlm.nih.gov/pubmed/15331575
704. Weinstein LS, Shenker A, Gejman PV, et al. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med. 1991;325:1688.
http://www.ncbi.nlm.nih.gov/pubmed/1944469
705. Wells SA Jr, Doherty GM. The surgical management of hyperparathyroidism. In: Bilezikian JP, Marcus R, Levine MA, eds. The Parathyroids: Basic and Clinical Concepts. San Diego: Academic Press; 2001:487.
706. Welt LG, Gitelman H. Disorders of magnesium metabolism. Dis Mon. 1965;1:1.
http://www.ncbi.nlm.nih.gov/pubmed/14294876
707. Wen SF. Micropuncture studies of phosphate transport in the proximal tubule of the dog. The relationship of sodium reabsorption. J Clin Invest. 1974; 53:143.
http://www.ncbi.nlm.nih.gov/pubmed/4808634
708. Werner A, Kempson SA, Biber J, et al. Increase of Na/P_i -cotransport encoding mRNA in response to low P_i diet in rat kidney cortex. J Biol Chem. 1994; 269:6637.
http://www.ncbi.nlm.nih.gov/pubmed/8120016
709. Werner A, Moore ML, Mantei N, et al. Cloning and expression of cDNA for a Na/Pi cotransport system of kidney cortex. Proc Natl Acad Sci. USA 1991;88:9608.
710. Whang R, Oei TO, Hamiter T. Frequency of hypomagnesemia associated with hypokalemia in hospitalized patients. Am J Clin Pathol. 1979;71:610.
711. Whang R, Welt LG. Observations in experimental magnesium depletion. J Clin Invest. 1963;42:305.
http://www.ncbi.nlm.nih.gov/pubmed/13976753
712. White KE, Carn G, Lorenz-Depiereux B, et al. Autosomal-dominant hypophosphatemic rickets (ADHR) mutations stabilize FGF-23. Kidney Int. 2001; 60:2079.
http://www.ncbi.nlm.nih.gov/pubmed/11737582
713. White KE, Jonsson KB, Carn G, et al. The autosomal dominant hypophosphatemic rickets (ADHR) gene is a secreted polypeptide overexpressed by tumors that cause phosphate wasting. J Clin Endocrinol Metab. 2001;86:497.
http://www.ncbi.nlm.nih.gov/pubmed/11157998
714. Windhager EE, Frindt G, Milovanovic S. The role of Na-Ca exchange in renal epithelia: an overview. Ann N Y Acad Sci. 1991;639:577.
http://www.ncbi.nlm.nih.gov/pubmed/1785887
715. Winnacker JL, Becker KL, Katz S. Endocrine aspects of sarcoidosis. N Engl J Med. 1968;278:427.
http://www.ncbi.nlm.nih.gov/pubmed/4867234
716. Woda CB, Halaihel N, Wilson PV, et al. Regulation of renal NaPi-2 expression and tubular phosphate reabsorption by growth hormone in the juvenile rat. Am J Physiol Renal Physiol. 2004;287:117.
http://www.ncbi.nlm.nih.gov/pubmed/14996669
717. Wong NL, Quamme GA, O'Callaghan TJ. Renal tubular transport and phosphate depletion: A micropuncture study. Can J Physiol Pharmacol. 1980;58:1063.
718. Wong NLM, Quamme GA, Dirks JH. Tubular reabsorptive capacity for magnesium in the dog kidney. Am J Physiol. 1983;224:62.
http://www.ncbi.nlm.nih.gov/pubmed/6849387
719. Wu KI, Bacon RA, Al-Mahrouq HA, et al. Nicotinamide as a rapid-acting inhibitor of renal brush-border phosphate transport. Am J Physiol. 1988;255:15.
http://www.ncbi.nlm.nih.gov/pubmed/2839989
720. Wysolmerski JJ, Broadus AE. Hypercalcemia of malignancy: the central role of parathyroid hormone-related protein. Ann Rev Med. 1994;45:189.
http://www.ncbi.nlm.nih.gov/pubmed/8198376

721. Wysolmerski JJ, Stewart AF. The physiology of parathyroid hormone-related protein: An emerging role as a developmental factor. Annu Rev Physiol. 1998;60:431.
http://www.ncbi.nlm.nih.gov/pubmed/9558472
722. Xu H, Bai L, Collins JF, et al. Age-dependent regulation of rat intestinal type IIb sodium-phosphate cotransporter by 1,25-(OH)(2) vitamin D(3). Am J Physiol Cell Physiol. 2002;282:487.
723. Xu H, Inouye M, Hines ER, et al. Transcriptional regulation of the human NaPi-IIb cotransporter by EGF in Caco-2 cells involves c-myb. Am J Physiol Cell Physiol. 2003;284:1262.
724. Xu H, Uno JK, Inouye M, et al. Regulation of intestinal NaPi-IIb co-transporter gene expression by estrogen. Am J Physiol Gastrointest Liver Physiol. 2003;285:1317.
http://www.ncbi.nlm.nih.gov/pubmed/12893629
725. Yamashita T, Konishi M, Miyake A, et al. Fibroblast growth factor (FGF)-23 inhibits renal phosphate reabsorption by activation of the mitogen-activated protein kinase pathway. J Biol Chem. 2002;277:28265.
http://www.ncbi.nlm.nih.gov/pubmed/12032146
726. Yamazaki Y, Okazaki R, Shibata M, et al. Increased circulatory level of biologically active full-length FGF-23 in patients with hypophosphatemic rickets/osteomalacia. J Clin Endocrinol Metab. 2002;87:4957.
http://www.ncbi.nlm.nih.gov/pubmed/12414858
727. Yang JM, Lee CO, Windhager EE. Regulation of cytosolic free calcium in isolated perfused proximal tubules of Necturus. Am J Physiol. 1988;255: F787.
http://www.ncbi.nlm.nih.gov/pubmed/3177659
728. Yu ASL, Hebert SC, Brenner BM, et al. Molecular characterization and nephron distribution of a family of transcripts encoding the pore-forming sub- unit of Ca^{2+} channels in the kidney. Proc Natl Acad Sci U S A. 1992;89:10494.
http://www.ncbi.nlm.nih.gov/pubmed/1279681
729. Yusuf AN, Murayama N, Keller MJ, et al. Modulatory effect of thyroid hormones on uptake of phosphate and other solutes across luminal brush border membrane of kidney cortex. Endocrinology. 1985;116:2438.
http://www.ncbi.nlm.nih.gov/pubmed/2986951
730. Zamkoff KW, Kirshner JJ. Marked hypophosphatemia associated with acute myelomonocytic leukemia: Indirect evidence of phosphorus uptake by leukemic cells. Arch Intern Med. 1980;140:1523.
731. Zazzo J-F, Troche G, Ruel P, et al. High incidence of hypophosphatemia in surgical intensive care patients: efficacy of phosphorus therapy on myocardial function. Intensive Care Med. 1995;21:826.
http://www.ncbi.nlm.nih.gov/pubmed/8557871
732. Zerwekh JE, Sanders LA, Townsend J, et al. Tumoral calcinosis: evidence for concurrent defects in renal tubular phosphorus transport and in 1alpha,25-dihydroxycholecalciferol synthesis. Calcif Tissue Int. 1980;32:1.
http://www.ncbi.nlm.nih.gov/pubmed/6775776
733. Zlot C, Ingle G, Hongo J, et al. Stanniocalcin 1 is an autocrine modulator of endothelial angiogenic responses to hepatocyte growth factor. J Biol Chem. 2003;278:47654.
http://www.ncbi.nlm.nih.gov/pubmed/14500721
734. Zusman J, Brown DM, Nesbit ME. Hyperphosphatemia, hyperphosphaturia and hypocalcemia in acute lymphoblastic leukemia. N Engl J Med. 1973;289:1335.
http://www.ncbi.nlm.nih.gov/pubmed/4518614