Phosphorus Metabolism and its Disorders in Childhood

JOSEPH M. GERTNER, MB, MRCP

Phosphorus plays a critical role in the physiology of all living creatures. Although often considered one of the bone-mineral elements, its role extends far beyond bone mineralization. Phosphorus is a key component of the nucleic acids which control the transmission of genetic instruction. Phosphorus is essential for many aspects of intermediary metabolism and is included in the lipoproteins forming the membranes of cells and intracellular organelles. The multiple roles for phosphorus in the body economy may explain the development of powerful systems designed to conserve phosphorus. A variety of disease states can arise as a consequence of failure of these control systems.

Conventionally, phosphate concentrations are expressed in terms of the concentration of elemental phosphorus. In the absence of pH changes, knowledge of total plasma inorganic phosphate (plasma phosphorus) provides adequate physiological information. While total body phosphorus content is tightly regulated, serum phosphorus levels vary widely. In childhood, serum phosphorus levels are age-dependent1 (Figure 1).

RENA L CONTROL

Unlike calcium, which is regulated by alterations in bone metabolism and by adjustments in the rate of intestinal absorption, the fraction of ingested phosphorus absorbed from the diet is relatively constant.

Although often considered one of the bone-mineral elements, the role of phosphorus extends far beyond bone mineralization.

Phosphorus homeostasis is largely under renal control, and the rate of proximal tubular phosphate reabsorption is the main factor governing fasting serum phosphorus levels. Reabsorption proceeds via a sodium-dependent mechanism related to the carrier system responsible for glucose reabsorption. The rate of renal phosphate reabsorption is controlled by hormones, but other control mechanisms, such as the one which links renal phosphate conservation to dietary phosphorus intake, also exist.

HORMONAL AND DIETARY CONTROL

Parathyroid Hormone

Parathyroid hormone (PTH) plays an important role in renal phosphate handling and hence in phosphorus homeostasis in general. The signal to which PTH secretion responds, however, is calcium, not phosphorus concentration, so that this system does not act primarily in defense of plasma phosphorus.

Other Hormones

Humoral factors other than those depending on dietary intake and PTH secretion affect renal phosphate handling, but their importance is unclear. These factors include growth hormone, insulin, possibly the insulin-like growth factors/somatotropins, epinephrine, estrogens, and calcitonin. The vitamin D

Dr. Gertner is Program Director and Associate Professor of Pediatrics, The New York Hospital-Cornell Medical Center, New York, New York.
Address reprint requests to Joseph M. Gertner, MB, MRCP, Program Director, Department of Pediatrics, The New York Hospital-Cornell Medical Center, 525 East 68th Street, New York, NY 10021.
metabolites seem to play only a small part in phosphate homeostasis. The effects of these hormones on renal phosphate handling are shown in Table 1.

**Diet**

Dietary phosphorus intake has an even greater effect than PTH on renal phosphorus handling. Phosphate loading decreases tubular phosphate reabsorption, whereas phosphorus restriction can rapidly and sharply reduce urinary phosphorus excretion. Phosphorus conservation during phosphorus deprivation is not PTH-dependent, because it occurs in the absence of parathyroids. The renal capacity to conserve phosphorus depends on bodily phosphorus needs, as well as supply. Total starvation will not increase phosphate reabsorption; this only occurs if enough energy and nitrogen for protein synthesis are provided during phosphorus restriction. Growing children, children receiving growth hormone, and adults with acromegaly all have higher renal thresholds for phosphorus (and serum phosphorus concentrations) than do healthy adults.

**DISORDERS OF PHOSPHATE CONTROL**

**Hyperphosphatemia**

Hyperphosphatemia can result from excessive phosphorus intake or from a reduced renal clearance of phosphorus. Acutely, hyperphosphatemia can lead to hypocalcemia by disturbing the equilibrium between ionic calcium and phosphate in the extracellular fluid and insoluble calcium phosphate (Table 2). Hyperphosphatemia also inhibits renal activation of calcidiol to calcitriol and this tends to diminish plasma calcium. The symptoms of acute hyperphosphatemia are all due to hypocalcemia: jittery movements and convulsions in the newborn, and painful limb spasms (tetany) in older children.

**Excessive Phosphorus Intake**

In the newborn, acute phosphorus overload may cause hypocalcemia, as when babies are fed with cow’s milk or inadequately modified milk-based formulas. Cow’s milk contains six times as much phosphorus as does human milk (950 v 162 mg/L). Ingestion of a calorically adequate volume of cow’s milk overwhelms the capacity of the neonatal kidney to excrete phosphate, resulting in hyperphosphatemia.
PHOSPHORUS METABOLISM

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Although chronic excessive phosphorus ingestion does not lead to hyperphosphatemia, it may lead to harmful disturbances in bone mineral metabolism. Particular concern has been voiced with regard to soft drinks of the cola variety, which contain up to 60 mg of elemental phosphorus per can. Overindulgence in these drinks may reduce calcium absorption from the intestine, reducing skeletal mineral accretion at a critical phase during adolescence and possibly predisposing to late osteoporosis. More research is clearly needed in this area of adolescent nutrition.

In older children and adults, it is almost impossible to produce a state of phosphate intoxication as a result of excessive oral intake. Acute hyperphosphatemia has, however, been described in children who had retained large volumes of phosphorus-containing enemas.

**Diminished Renal Phosphate Excretion**

**Uremia.** Glomerular renal failure is a major cause of excessive phosphorus retention.

**Hypoparathyroidism (HP).** PTH normally has a marked phosphaturic effect. Parathyroid failure and resistance to PTH are, therefore, important causes of hyperphosphatemia due to increased renal phosphate reabsorption. Some of the causes and associated clinical features are listed in Table 3. Congenital disorders often present in young children, while acquired disease is seen later, as an accompaniment to pathological or iatrogenic parathyroid destruction. These conditions generally present with hypocalcemia and hyperphosphatemia. PTH levels are low or undetectable, and urinary cyclic adenosine monophosphate (AMP) excretion is low, as are serum calcitriol levels. There may be ectopic calcification in the skin and, characteristically, in the basal ganglia of the brain.

**Pseudohypoparathyroidism (Php).** In pseudohypoparathyroidism, tissues show a variable degree of resistance to PTH. Php was first described by Albright in patients showing a distinctive phenotype of short fourth metacarpals (brachydactyly), round facies, short stature, and mental retardation (Albright's hereditary osteodystrophy [AHO]). It is now known to comprise a number of distinct entities. The physical appearance may be completely normal. The distinction between HP and Php is the level of circulating immunoreactive PTH, which is low in HP and high in Php.

In type I Php, tissues normally containing a PTH-sensitive adenylyl cyclase fail to generate cyclic AMP upon exposure to PTH. Type II Php is a very rare condition in which the phosphaturic response to PTH is absent, although cyclic AMP response is normal.

In type I Php, a dynamic test of the biochemical response to PTH can be performed by injecting PTH intravenously and measuring the urinary cyclic AMP:creatinine ratio. This rises 20- to 40-fold in normal subjects, but not more than two- to threefold in Php.

**Tumoral Calcinosis.** This is a familial (dominant) condition in which renal phosphate reabsorption is excessive despite normal parathyroid responsiveness and near-normal calcitriol metabolism. The name arises from the massive deposits of soft-tissue calcification that may occur, especially in and near joints (Figure 2). Treatment with dietary phosphorus deprivation has been tried, but is rarely effective.

**Hyperparathyroidism** is very rare in childhood. Secondary hyperparathyroidism is seen in vitamin D-
TABLE 3

FEATURES OF CHILDHOOD HYPOPARATHYROIDISM

<table>
<thead>
<tr>
<th>Type</th>
<th>Parathyroid Pathology</th>
<th>Age of Onset</th>
<th>Associated Features</th>
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</thead>
<tbody>
<tr>
<td>Temporary hypoparathyroidism</td>
<td>Fetal parathyroid suppression</td>
<td>Birth</td>
<td>Maternal hypercalcemia</td>
</tr>
<tr>
<td>DiGeorge syndrome</td>
<td>Congenital absence of parathyroids</td>
<td>Birth</td>
<td>T cell dysfunction, thymic aplasia, congenital heart disease</td>
</tr>
<tr>
<td>Isolated congenital hypoparathyroidism</td>
<td>Absence of parathyroids</td>
<td>0-5</td>
<td>Occasionally familial</td>
</tr>
<tr>
<td>Candida endocrinopathy</td>
<td>Autoimmune destruction</td>
<td>5-15</td>
<td>Mucocutaneous candidiasis, hypoadrenalism</td>
</tr>
<tr>
<td>Hemosiderosis</td>
<td>Iron deposition</td>
<td>15-25</td>
<td>Transfusion-treated thalassemia major</td>
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<tr>
<td>Postsurgical</td>
<td>Ischemic necrosis</td>
<td>10+</td>
<td>Surgery for thyrotoxicosis or thyroid cancer</td>
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<tr>
<td>Magnesium depletion</td>
<td>Reduced PTH secretion</td>
<td>Any</td>
<td>Gut fistulae, steatorrhea</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td>Peripheral resistance to PTH</td>
<td>5-10</td>
<td>Moon facies, brachydactyly, short stature</td>
</tr>
</tbody>
</table>

Figure 3. Hypophosphatemic rickets. The patient’s mother and other family members are affected by this X-linked condition. Note that nutritional state is quite good.

deficiency rickets and in uremia. Tertiary hyperparathyroidism describes autonomous hypersecretion in glands subject to prolonged stimulation which may occur during therapy for familial hypophosphatemic rickets or uremia.

Primary hyperparathyroidism may arise from hyperplasia of all the parathyroid glands or from the development of tumors in one or more of the glands. Childhood cases are usually associated with one of three familial syndromes: severe neonatal hyperparathyroidism, or multiple endocrine neoplasia, types 1 and 2.5,6

Patients with hyperparathyroidism are hypercalcemic due to the increased bone resorption and increased calcium absorption which follows enhanced PTH-mediated calcitriol synthesis. Serum phosphorus is low because PTH decreases renal tubular reabsorption of phosphate. Serum PTH levels and urinary cyclic AMP excretion are increased.

Treatment of primary and tertiary hyperparathyroidism is surgical. Secondary hyperparathyroidism should respond to correction of the underlying cause.

Excessive renal phosphate loss in childhood causes poor skeletal mineralization, resulting in rickets. Rickets is confined to childhood, when the skeleton is growing, and affects only the growth plate. The adult equivalent is a general skeletal softening known as osteomalacia. Children with rickets often also suffer from osteomalacia, so that the shafts of the long bone continued on page 964
TABLE 4

<table>
<thead>
<tr>
<th>BIOCHEMICAL ASSOCIATIONS OF CHILDHOOD RICKETS</th>
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<tbody>
<tr>
<td>Type of Rickets</td>
</tr>
<tr>
<td>Vitamin D deficient</td>
</tr>
<tr>
<td>Vitamin D dependent</td>
</tr>
<tr>
<td>Type I</td>
</tr>
<tr>
<td>Type II*</td>
</tr>
<tr>
<td>Fanconi syndrome</td>
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<tr>
<td>Familial hypophosphatemia</td>
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<tr>
<td>Renal tubular acidosis</td>
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<tr>
<td>Uremic osteodystrophy</td>
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* Often occurs with alopecia.  
† PTH may rise during therapy.

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as well as the growth plates are affected. Features of rickets include:
• widening and flaring of the epiphyses;
• frontal bossing (when onset is in infancy);
• expanded costo-chondral junctions;
• peri-articular swelling at ankles, wrists, and knees. 
The severity of involvement of particular epiphyses and the nature of the deformity (eg, genu valgum or varum) depends on the relative growth rate, which varies with age (Figure 3).

Rickets can be caused by a number of distinct abnormalities of vitamin D intake and metabolism, and of mineral homeostasis. The sources and metabolism of vitamin D are outlined in Figure 4. A summary of the biochemical findings is given in Table 4. A summary of the biochemical findings is given in Table 4.

Vitamin D Deficiency

Vitamin D metabolites play a role in the maintenance of extracellular fluid calcium and phosphorus and also act directly on skeletal tissues to aid mineralization.

Children with vitamin D-deficiency rickets may have bone pain, myopathy, and hypocalcemia. Causes include:
• nutritional deprivation;
• lack of sunlight;
• gastrointestinal and liver disease; and
• anti-convulsant therapy.

Treatment. Administration of 400 IU of vitamin D per day either directly or as a food supplement will prevent rickets. To treat established vitamin D deficiency administer vitamin D 1600 to 2000 IU daily unless intestinal malabsorption is present. Reduce to 400 IU per day when the rickets heals.

In cases of malabsorption, the replacement dose may be as high as 10,000 IU per day. Orthopedic surgery may be needed in severe cases.

Rickets of Prematurity

Premature babies may develop rickets, particularly when they require parenteral hyperalimentation.

Some otherwise healthy very low birth weight infants may also develop rickets, probably due to combined phosphorus and calcium deficiency.²

Treatment. We recommend dietary supplementation with calcium and phosphorus, eg, calcium glucosinate (Neocalglucan 60 mg elemental calcium/kg/day) and potassium phosphate (30 mg elemental phosphorus/kg/day).

Vitamin D supplements are not sufficient to prevent the rickets of prematurity. Although bone problems in premature infants have frequently been observed, they do not usually persist into childhood. Further follow-up is necessary to determine whether prematurity predisposes to bone disease in later life.

TABLE 5

CAUSES OF HYPOPHOSPHATEMIA

<table>
<thead>
<tr>
<th>Inadequate intake</th>
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<tbody>
<tr>
<td>Overuse of phosphate-binding antacids</td>
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<td>Total parenteral nutrition</td>
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<table>
<thead>
<tr>
<th>Excessive renal loss</th>
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<tbody>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Isolated renal phosphate loss</td>
</tr>
<tr>
<td>Familial</td>
</tr>
<tr>
<td>Acquired</td>
</tr>
<tr>
<td>Proximal renal tubular failure (Fanconi)</td>
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</tbody>
</table>

Hypophosphatemic Rickets

Rickets in childhood hypophosphatemia has many causes (Table 5). Its most common form is familial hypophosphatemic rickets (FHR), a condition dominated by proximal renal tubular phosphate wasting. Apart from phosphate wasting, renal glomerular and tubular function is normal. FHR is inherited as an X-linked dominant, but many cases have no family history and, presumably, represent new mutations.

Rickets appears in the first year of life. Vitamin D metabolite levels are usually normal, while PTH may lie in the high to normal range.

Treatment. Since this disease is primarily due to phosphate wasting, a sensible approach is to give large
Figure 4. Steps in the formation of the vitamin D hormone, 1,25(OH)2D. The + sign above PTH and the − sign over P, and Ca++ indicate, respectively, enhancement by PTH and inhibition by calcium and inorganic phosphate, of the final conversion step from 25 OH D to 1,25(OH)2D.

amounts of phosphate orally, up to 2.5 g per day. It is important to spread the doses evenly throughout the 24 hour period and not to allow a lapse period of greater than 8 hours each night. Oral phosphate alone may lead to secondary hyperparathyroidism, therefore, a combination of vitamin D and oral phosphorus is now used. Vitamin D counters the tendency of phosphate therapy to lead to secondary hyperparathyroidism and may have a directly beneficial effect on bone. Calcitriol is the preferred vitamin D metabolite, because its short half-life (14 to 18 hours) guards against overdosage during the treatment of hypercalcemia. In addition, calcitriol may have a more powerful and direct effect on bone than does vitamin D itself.

REFERENCES