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## Hypophosphatemic Disorders

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# Hypophosphatemic Disorders

Stanley Goldfarb, MD

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## INTRODUCTION

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Phosphorus is one of the most abundant elements found in tissue and is a major mineral component of bone. It is a key factor in metabolic processes and in maintenance of cell membrane structure. Almost all metabolic processes are critically dependent on phosphorus, particularly the provision of cellular energy in the form of adenosine triphosphate (ATP) and the phosphorylation of various enzymes (eg, protein kinases). The latter are involved in the expression of the cellular effects of hormones and other signaling molecules. Phosphorus is an important constituent of membrane phospholipids, which play an essential role in cell membrane integrity and in regulation of the phosphoinositide system, a critical regulatory and signaling system in cell homeostasis. In addition, phosphorus may influence the oxygen-carrying capacity of hemoglobin through regulation of 2,3-diphosphoglycerate (2,3-DPG) synthesis.

This review discusses the pathophysiology of phosphate metabolism, with an emphasis on the disorders that lead to hypophosphatemia and its manifestations. It has been customary to express concentrations in terms of elemental phosphorus but to refer to it as phosphate; this practice will be followed throughout this review.

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## PHOSPHATE METABOLISM AND HANDLING

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### TOTAL BODY CONTENT AND INTAKE

Total body content of phosphate is approximately 1000 g; approximately 85% of this amount is contained within bone mineral and most of the remainder is intracellular. Of the total plasma inorganic phosphate, approximately 10% is bound to protein, 5% is complexed, and the remainder is in the form of orthophosphates.

The normal fasting serum level of phosphate in adults is 3.0 to 4.5 mg/dL, or 0.7 to 1.1 mmol/L. This level is higher in children and postmenopausal women. Ingestion of carbohydrates lowers the serum phosphate concentration by enhancing cellular uptake, and, con-

versely, ingestion of phosphate-rich foods results in an acute elevation of serum phosphate. Therefore, to obtain an accurate assessment of phosphate serum levels, plasma and urine samples should be drawn from patients in the fasting state.

The average daily intake of phosphorus in the United States is about 1000 mg, mostly provided by dairy products, meats, eggs, and to a lesser extent, vegetables and grains. The absorption mechanism in the small intestine is complex, but the largest component of dietary phosphate is absorbed by passive diffusion. The net amount of phosphate absorbed daily from the gastrointestinal tract is approximately 700 mg. The gastrointestinal tract also secretes a relatively fixed amount of phosphate, about 200 mg per day, that appears in stools. To maintain normal external balance at stasis, adults must excrete in the urine an amount equal to net intestinal absorption every day.

### RENAL HANDLING OF PHOSPHATE

The kidney filters some 8000 mg of phosphate daily and excretes an amount equal to net intake. Phosphate regulation occurs primarily in the proximal tubule.<sup>1</sup> The key element that determines the rate of renal reabsorption of phosphate is the sodium/phosphate cotransporter, a protein that spans 8 transmembrane domains.<sup>2</sup> **Figure 1** shows a model of proximal tubule phosphate transport at baseline: the sodium/phosphate cotransporter is formed in the endoplasmic reticulum of the proximal tubule cell, inserted into the apical membrane, and then degraded in subapical vesicles. The energy driving phosphate transport is derived from the gradient for sodium from the apical side into the cell. As sodium and phosphate enter the cell, the powerful  $\text{Na}^+, \text{K}^+$ -ATPase pump on the basolateral membrane extrudes sodium from the cell and recreates the gradient, allowing further sodium and associated phosphate to enter through the cotransport protein.

Two primary factors govern the rate of proximal tubular phosphate transport, parathyroid hormone (PTH) and dietary phosphate.<sup>3,4</sup> **Figure 2** shows how the action of PTH is manifest at the cellular level. PTH secreted from the parathyroid glands is released into the circulation, where it binds to its receptor and increases