

The Essentials of Calcium, Magnesium and Phosphate Metabolism: Part I. Physiology

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ABSTRACT

Objective: *To review the components of calcium, phosphate and magnesium metabolism that are relevant to the critically ill patient in a two-part presentation.*

Data sources: *A review of articles reported on calcium, phosphate and magnesium disorders in the critically ill patient.*

Summary of review: *Calcium, phosphate and magnesium have important intracellular and extracellular functions with their metabolism often linked through common hormonal signals. A predominant portion of total body calcium is unionised within bone and serves an important structural function. Intracellular and extracellular ionised calcium changes are often linked and have important secretory and excitatory roles. The extracellular ionised calcium is carefully regulated by parathyroid hormone and vitamin D, whereas calcitonin is secreted largely in response to hypercalcaemia.*

Phosphorous is needed for bone structure although it also has an important role in cell wall structure, energy storage as ATP, oxygen transport and acid-base balance. Ionised calcium, in as far as it controls PTH secretion, indirectly controls urinary phosphate excretion. When plasma phosphate increases, tubular reabsorption also increases up to a maximum ($TmPO_4$), thereafter phosphate is excreted. The minimum oral requirement for phosphate is about 20 mmol/day.

Magnesium is a predominantly intracellular ion that acts as a metallo-coenzyme in more than 300 phosphate transfer reactions and thus has a critical role in the transfer, storage and utilisation of energy within the body. Extracellular magnesium concentrations are largely controlled by the kidneys with the renal tubular maximum reabsorption ($TmMg$) controlling the plasma magnesium concentration.

Conclusions: *In the critically ill patient calcium, magnesium and phosphate metabolism, are often disturbed with an alteration in intake, increased liberation from bone and damaged tissue and reduced excretion (e.g. during renal failure), causing alterations in extracellular concentrations and subsequent disordered organ function. (Critical Care and Resuscitation 2002; 4: 301-306)*

Key words: Calcium, phosphate, magnesium, vitamin D, parathyroid hormone, calcitonin

CALCIUM METABOLISM

The extracellular fluid (ECF) ionised calcium (1 mmol/L) concentration is 10^4 times the concentration of the intracellular fluid (ICF) ionised calcium with the latter varying during normal function by up to 10-fold (e.g. from 10^{-4} to 10^{-3} mmol/L). Nonionised calcium is

predominantly found in bone providing an important structural function to the human body, whereas the ionised calcium is responsible for a variety of physiological effects that are characteristic of the cell type (e.g. secretion, neuromuscular impulse formation, contractile functions, clotting).

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The distribution of total body calcium in a 70 kg man is shown in Table 1. Normal plasma calcium, which consists of protein bound, ionised and complexed calcium, ranges from 2.10 - 2.55 mmol/L. Normal plasma ionised calcium ranges from 1.15 - 1.30 mmol/L. If the total plasma calcium is 2.45 mmol/L then the distribution of plasma calcium is approximately:

- 1.0 mmol/L protein bound (i.e., 40% of the total plasma calcium; 80% of which is bound to albumin and 20% of which is bound to globulins),
- 1.15 mmol/L ionised (i.e. 47% of the total plasma calcium) and,
- 0.3 mmol/L complexed with plasma bicarbonate, lactate, citrate, phosphate and sulphate (i.e. 13% of the total plasma calcium).

Table 1. Distribution of total body calcium in a 70 Kg man

	mmol
Bone and teeth (nonexchangeable)	30 000
(exchangeable)	100
Extracellular fluid	
Interstitial fluid	23
Plasma	12
Total	30,135

While the plasma ionised calcium can be directly measured, the total plasma calcium is commonly measured, which varies with the variation in plasma protein levels. A correction factor of 0.02 mmol/L added to the measured calcium level for every 1 g/L increase in plasma albumin (up to a value of 40 g/L), may be used to calculate the effect of plasma albumin on total plasma calcium (e.g. if the measured total plasma calcium is 1.83 mmol/L and plasma albumin is 25 g/L, the corrected plasma calcium is, $1.83 + (40 - 25) \times 0.02$ mmol/L = 2.13 mmol/L). The correction factor for globulin is 0.004 mmol/L for each 1 g/L rise in globulin.

However, in critically ill patients, there are large variations in ionised calcium due to:

- a) pH alterations in calcium binding by albumin (e.g. for every 0.1 unit reduction in plasma pH, the albumin bound calcium decreases by 0.07 mmol/L and ionised calcium increases by 0.07 mmol/L) and
- b) alterations in calcium complexed with:
 - 1) lactate (e.g. for each 1 mmol/L increase in lactate the ionised calcium decreases by 0.006 mmol/L, due largely to an increase in unionised calcium lactate, although lactic acidosis in patients with a

normal ventilatory response and previously normal albumin and bicarbonate levels usually has little effect on ionised calcium levels¹) and

- 2) bicarbonate (e.g. for each 1 mmol/L decrease in bicarbonate, the ionised calcium increases by 0.004 mmol/L, due largely to a liberation of Ca^{2+} from unionised calcium bicarbonate).²

Therefore in the critically ill patient, for an accurate assessment of plasma ionised calcium status, direct measurement of the ionised calcium should be performed,^{3,4} and is often readily available (using an ion specific electrode) in association with standard blood gas estimations.

Numerous hormones can influence calcium metabolism (e.g. 1,25 dihydroxycholecalciferol, parathyroid hormone, calcitonin, parathyroid hormone related protein, oestrogen, corticosteroids, thyroxin, growth hormone) although only 1,25 dihydroxycholecalciferol, parathyroid hormone, calcitonin are primarily concerned with the regulation of calcium metabolism.

Daily calcium balance

Of the 20 mmol of calcium ingested daily, approximately 40% (i.e. 8 mmol) is absorbed in the duodenum and upper jejunum, although this varies from 10 - 90% (2 - 18 mmol) depending on the circulating level of 1,25 dihydroxycholecalciferol ($1,25(\text{OH})_2\text{D}_3$). About 10% of calcium absorption occurs by passive diffusion. The bone liberates and reabsorbs approximately 500 mmol of calcium per day from an exchangeable pool of 100 mmol. The minimum daily requirement of calcium for an healthy adult is about 5 mmol.⁵

About 250 mmol of ionised calcium is filtered by the kidneys daily. About 65% (i.e. 170 mmol) of the filtered load is passively reabsorbed with sodium in the proximal tubule, 20% (i.e. 50 mmol) is reabsorbed in the thick ascending loop of Henle and 10% (i.e. 25 mmol) is absorbed in the distal nephron. Parathyroid hormone (PTH) increases calcium absorption in the thick ascending loop of Henle as well as in the distal convoluted tubule. PTH has no effect on calcium reabsorption in the proximal tubule. The urinary excretion of calcium is 2.5 - 7.5 mmol per day and represents about 3 - 5% of the filtered calcium.⁵ Approximately 60% (i.e. 12 mmol) of the oral daily intake is excreted with the faeces.

Regulation of ionised calcium in the extracellular fluid

In health, the plasma ionised calcium does not vary by more than 5% and is maintained largely by the actions of PTH and vitamin D. Calcitonin does not

normally regulate plasma calcium levels and is only secreted when hypercalcaemia exists.

Parathyroid hormone

Parathyroid hormone (PTH) is an 84 amino acid polypeptide that has a molecular weight of 9500, a plasma half-life of 10 min (PTH is cleaved by hepatic Kupffer cells and the fragments are excreted by the kidneys) and a plasma level that varies between 1.0 and 6.5 pmol/L. It is synthesised as part of a larger molecule containing 115 amino acid residues (preproPTH) which is modified to form proPTH by the removal of 25 amino acids. Finally PTH is formed by the removal of 6 amino acid residues and is packed in secretory granules. The main factor controlling the secretion of PTH is plasma ionised calcium, stimulating the calcium-sensing receptor on the cell membrane of the parathyroid chief cell to inhibit secretion of PTH with hypercalcaemia and promote secretion of PTH with hypocalcaemia.^{6,7} The production of PTH is inhibited by 1,25 (OH)₂D₃.⁸ The main sites of PTH action are in bone and kidney. Magnesium is also required for normal PTH function as hypomagnesaemia can cause hypocalcaemia due to impaired synthesis and/or release of PTH and impaired peripheral action of PTH.⁹

Bone. PTH acts on an osteoblast cell membrane receptor, activating adenylate cyclase and increasing intracellular cAMP, which increases the cell permeability to calcium. The increase in cytosolic calcium activates a pump that drives calcium from the bone to the ECF. The pump is enhanced by 1,25 (OH)₂D₃.^{8,10} An increase in the activity of the pump is associated with an increase in plasma alkaline phosphatase.

Kidney. PTH acts on a renal tubule membrane receptor, activating adenylate cyclase and increasing intracellular (and urine) cAMP which, in turn, decreases proximal renal tubule phosphate (as well as HCO₃⁻) reabsorption. PTH also increases distal nephron calcium reabsorption and stimulates the 1 α -hydroxylase conversion of 25 hydroxycholecalciferol (25 (OH)D₃) to 1,25 (OH)₂D₃, thereby acting indirectly on the gastrointestinal tract by increasing absorption of calcium.¹¹

Vitamin D

The term vitamin D refers to a group of fat soluble vitamins produced by the action of ultraviolet light on 7-dehydrocholesterol on the skin surface to form vitamin D₃ (cholecalciferol). Vitamin D₃ and D₂ are ingested in the diet, and in countries where exposure to sunlight is reduced, steatorrhoea can cause rickets or osteomalacia.

Intake. The average daily intake of vitamin D is 500 IU. The daily requirement is 100 IU, although the

recommended intake is 400 IU/day (1 mg of vitamin D₃ = 40 000 IU).

Metabolism. Vitamin D₃ is converted to 25 (OH)D₃ in the liver, and transported in the blood bound to an alpha-2-macroglobulin (vitamin D-binding protein). This metabolic step is not tightly regulated and the circulating 25(OH)D₃ functions mainly as a vitamin D₃ store. The plasma half-life of 25(OH)D₃ is 15 days. It is converted to either 1,25 (OH)₂D₃, by a 1 α -hydroxylase in the renal tubular cells of the distal part of the proximal convoluted and straight tubule, or to the poorly active metabolite, 24,25 (OH)₂D₃.^{8,12} The latter is an escape route for 25(OH)D₃ metabolism when no further 1,25 (OH)₂D₃ is required. The biological activity of 1,25 (OH)₂D₃ is 500-1000 times greater than its precursor 25(OH)D₃, and has a half-life of 15 hr. Extrarenal 1,25 (OH)₂D₃ production can also occur in the macrophage in granulomatous diseases (e.g. in sarcoidosis when the pulmonary macrophage is stimulated by γ -interferon).⁸

Regulation. The formation of 1,25 (OH)₂D₃ is regulated principally by 1,25 (OH)₂D₃ and PTH.⁸ PTH stimulates and 1,25 (OH)₂D₃ suppresses the activity of the 1 α -hydroxylase. Hypophosphataemia also stimulates the hydroxylase, whereas the effect of calcium on the enzyme is probably secondary to its effect on PTH levels (Figure 1).⁸ Growth hormone, insulin and prolactin also stimulate the activity of the 1 α -hydroxylase. The normal plasma level of 25(OH)D₃ ranges between 40 -160 nmol/L and the normal plasma level of 1,25 (OH)₂D₃ ranges between 40 - 150 pmol/L.

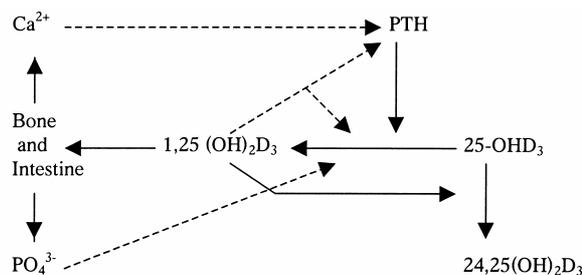


Figure 1. Renal tubule cell control of the formation of 1,25 dihydroxycholecalciferol. The solid lines represent stimulation. The dashed lines represent inhibition.

Actions. The major action of 1,25 (OH)₂D₃ is to increase the ECF calcium and phosphate by directly increasing calcium and phosphate absorption from the intestine. It does this by binding to a steroid receptor to alter mRNA transcription, with the mRNAs produced controlling formation of intracellular calbindin-D proteins (members of the troponin-C superfamily of calcium binding proteins that also includes calmodulin¹³). In the intestine, increases in calbindin-D9k and

calbindin-D28k levels are associated with an increase in calcium transport, although the exact mechanism as to how they facilitate calcium transport is unknown. The calbindin-D proteins can also increase intestinal absorption of magnesium, zinc, cobalt and strontium.

1,25 (OH)₂D₃ also facilitates normal osteoid mineralisation by providing sufficient concentrations of calcium and phosphate to the calcifying centres. It also demineralises osteoid by augmenting PTH action (although it also decreases PTH production by altering PTH gene transcription¹⁴) and may increase distal nephron calcium reabsorption¹⁵ by regulating the distal nephron intracellular calbindin-D28k levels.¹⁶

Calcitonin

Calcitonin is a 32 amino acid polypeptide hormone that has a molecular weight of 3500 and a half-life of less than 10 min.¹⁷ It is formed from the precursor procalcitonin (which has no known role in calcium metabolism). It is secreted by the C cells of the thyroid gland, predominantly when the plasma calcium is greater than 2.45 mmol/L (i.e. a plasma ionised calcium of 1.15 mmol/L). Therefore its major role appears to be the control of hypercalcaemia. Gastrin, glucagon, and beta-adrenergic agonists also stimulate calcitonin secretion, and may play a part in stimulating calcitonin and reducing the plasma calcium in acute illness. Calcitonin acts by almost completely inhibiting osteoclastic bone reabsorption, thereby reducing plasma calcium and phosphate levels without altering plasma magnesium levels.

Normal physiological events maintaining extracellular calcium and phosphate levels

1. If hypocalcaemia is present, this stimulates PTH secretion which in turn increases:

- a. Renal tubule calcium reabsorption and phosphate excretion
- b. The renal tubule 1 α -hydroxylase conversion of 25(OH)D₃ to 1,25 (OH)₂D₃ which increases gastrointestinal absorption of calcium and phosphate
- c. Osteoblast calcium and phosphate mobilisation from bone (enhanced by 1,25 (OH)₂D₃)

all of which increases the plasma calcium without increasing the plasma phosphate as the renal effect of PTH is to excrete excess phosphate.

2. If hypophosphataemia occurs, this stimulates the renal tubule 1 α -hydroxylase, thereby increasing 1,25 (OH)₂D₃ which stimulates gastrointestinal absorption of calcium and phosphate. The increase

in calcium inhibits PTH; thus renal retention of phosphate is high and calcium is low.

PHOSPHATE METABOLISM

Phosphate is needed for bone mineralisation and cellular structural components (e.g. phospholipids, nucleotides, phosphoproteins), for energy storage as ATP, for oxygen transport (in red blood cell 2,3-DPG) and for acid base balance (as a cellular and urinary buffer).^{5,18}

Phosphates in blood exist as either organic (ester and lipid phosphates) or inorganic compounds. Plasma phosphate measures the inorganic component. Total plasma phosphate in an adult ranges from 0.80 to 1.35 mmol/L. The range in children is 1.2 - 1.9 mmol/L due to the increased activity of growth hormone and reduced levels of gonadal hormones. The distribution of plasma phosphate between protein-bound, ionised and complexed forms when the total plasma phosphate is 1.00 mmol/L is:

- 15% protein bound (i.e. 0.15 mmol/L)
- 53% ionised (i.e. 0.45 mmol/L. The HPO₄²⁻:H₂PO₄⁻ ratio is 4:1 at a pH 7.4)
- 47% complexed with calcium or magnesium (i.e. 0.40 mmol/L)

Intracellular phosphate is approximately 100 mmol/L, with 5 mmol/L existing in the inorganic form and 95 mmol/L existing in the organic form (i.e. ATP, ADP, creatine phosphate, nicotinamide adenine dinucleotide). These intracellular forms are readily convertible.^{18,19} The distribution of total body phosphate in a 70 kg man is shown in Table 2.

Table 2. Distribution of total body phosphate in a 70 Kg man

	mmol	% total
Bone and teeth	19,300	85
Soft tissues	3,230	14.3
Interstitial fluid	7	0.03
Plasma	4	0.02
RBC	59	0.26
Total	22,600	

Daily phosphorous balance

The normal daily phosphate intake is approximately 40 mmol. Approximately, 60 - 70% (i.e. 25 - 30 mmol) is absorbed in the duodenum and upper jejunum.

Normal urinary phosphate excretion is 30 mmol/day (ranging between 10 and 40 mmol/day), 15 mmol/day is excreted with faeces. There is no tubular secretion of

phosphate. Of the 180 mmol/day of filtered phosphate, approximately 70 - 85% is reabsorbed in the proximal tubule and 20% is reabsorbed by the distal nephron. PTH induces phosphaturia by an inhibition of the sodium-phosphate cotransport in the proximal tubule.¹⁸ Ionised calcium, in as far as it controls PTH secretion, indirectly controls urinary phosphate excretion. When plasma phosphate increases then tubular reabsorption also increases up to a maximum (TmPO₄); thereafter phosphate is excreted. The TmPO₄ is decreased by PTH, renal vasodilation, saline and sodium bicarbonate. The minimum oral requirement for phosphate is about 20 mmol/day.⁵

MAGNESIUM METABOLISM

Magnesium is primarily an intracellular ion that acts as a metallo-coenzyme in over 300 phosphate transfer reactions. It participates in all reactions involving the formation and utilisation of ATP and thus has a critical role in the transfer, storage and utilisation of energy within the body. Magnesium is also required for protein and nucleic acid synthesis and for a number of mitochondrial reactions. While PTH and vitamin D do have minor effects on magnesium metabolism, these hormones do not regulate magnesium metabolism.²⁰

The exchangeable magnesium is approximately 2.5 mmol/kg. The total body distribution of magnesium is shown in Table 3.²¹

Table 3. Distribution of total body magnesium in a 70 kg man

	mmol
Bone	600
Intracellular (bound)	365
(free)	25
ECF	10
Total	1000

The total intracellular magnesium concentration is 15 mmol/L, whereas the ionised intracellular magnesium concentration ranges between 0.5 - 1.0 mmol/L.²² The plasma levels range from 0.70 - 0.95 mmol/L (i.e. the ionic concentrations of magnesium are approximately the same outside and inside the cell) which has a circadian rhythm with levels tending to be lowest from 1100 to 1600 hr.²³ The distribution of plasma magnesium between protein-bound, ionised and complexed forms when the plasma magnesium is 1 mmol/L is:²⁴

- 33% protein bound (i.e. 0.33 mmol/L, with 25% bound to albumin and 8% bound to globulin)

- 60% ionised (i.e. 0.60 mmol/L) and,
- 6% complexed with citrate, phosphate (i.e. 0.06 mmol/L).

Daily magnesium balance

The daily oral intake varies from 8 - 20 mmol, 40% (i.e. 3 - 8 mmol) of which is absorbed in the jejunum and ileum by passive absorption.

The urinary loss varies from 2.5 to 8 mmol/day.⁵ The glomerular filtration of magnesium is 100 mmol/day; 15% is absorbed in the proximal tubule, 70% is reabsorbed in the loop of Henle (most of which is reabsorbed in the thick ascending limb),^{25,26} 10% is reabsorbed in the distal tubule and 5% is usually excreted.²⁷ The maximum tubular reabsorption for magnesium (TmMg) is near the normal plasma magnesium levels, thus an increase in plasma magnesium is rapidly excreted by the kidney. In magnesium deficiency the renal loss can decrease to 0.05 - 0.10 mmol/day, and with normal renal function up to 200 mmol of Mg²⁺ may be excreted per day.²⁸ An increased urinary magnesium excretion also occurs with ECF volume expansion, hypercalcaemia, loop diuretics, phosphate depletion and alcohol ingestion.²⁹ The minimum daily requirement is approximately 0.5 mmol.³⁰

Received: 4 October 2002

Accepted: 22 November 2002

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