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Calcium, Phosphate and Magnesium Disorders

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Abstract

Calcium, phosphate and magnesium are essential for human function and life. Each electrolyte is readily found in the human diet, and homeostasis is tightly regulated by the intestine, kidney and bone as well as other critical hormones, receptors and transporters. Disturbance to this balance can result in symptomatic disease and life-threatening manifestations. Calcium and phosphate are particularly co-dependent with disruption to the balance of one often influencing the other. It is important that clinicians have a thorough understanding of the mechanisms underplaying the homeostasis of each electrolyte as they have implications for prevention and management of disease. This chapter aims to outline the importance of calcium, phosphate and magnesium; the regulation of each electrolyte and the consequences of imbalance.

Keywords: calcium, magnesium, phosphate, parathyroid hormone, fibroblast growth factor, vitamin D, hypercalcaemia, hypocalcaemia, hyperphosphataemia, hypophosphataemia, hypermagnesaemia, hypomagnesaemia

1. Introduction

Calcium, phosphate and magnesium are electrolytes essential to human function and life. The balance of each electrolyte is reliant on the interplay between the gastrointestinal tract, kidney and bone. Other hormones, receptors and transporters are also integral to calcium, phosphate and magnesium homeostasis, influencing the actions of the intestine, kidney and bone. This chapter will outline the importance of calcium, phosphate and magnesium, the mechanisms for regulation and the consequences of imbalance.

2. Calcium

2.1. The importance of calcium

The human body contains 1–2 kg of the divalent cation calcium. Greater than 99% of calcium is stored in bone, and this provides structure for the human skeleton. The remaining calcium is stored in the intracellular and extracellular space. Beyond its structural importance, calcium plays a role in functions including intracellular signalling, neuromuscular transmission, muscular function, endocrinological function, coagulation and intercellular adhesion [1].

Calcium homeostasis is maintained through a delicate relationship between organs, including the kidneys, intestine, parathyroid glands, and bone. This is mediated by hormones such as parathyroid hormone (PTH), vitamin D3 (cholecalciferol), calcitriol (1,25-dihydroxycholecalciferol), fibroblast growth factor 23 (FGF23) and klotho [2].

2.2. Dietary calcium

Calcium accumulation commences in the third trimester of pregnancy and increases during childhood, adolescence and into early adulthood, at which time calcium storage peaks. The net balance of calcium is determined by the difference between calcium intake and calcium loss.

Throughout childhood and early adulthood, a positive calcium balance is required for bone growth. In this age group, as little as 500 mg of dietary calcium intake results in a positive calcium balance and the efficiency of intestinal calcium absorption can accommodate for the amount of calcium intake [3]. Between 25 and 35 years of age, when bone growth is complete, the net calcium balance should be neutral. With ageing, bone mass decreases due to net resorption of bone at a rate of less than 1–2% per year [4]. However, menopause leads to a negative balance because of difficulties with intestinal absorption attributed to by oestrogen deficiency [2]. Postmenopausal women require 1200 mg of dietary calcium to achieve a positive calcium balance [3, 5].

2.3. Physiology of calcium

Calcium exists in the human body stored as bone (calcium hydroxyapatite) and is otherwise found in the extracellular or intracellular space. One percent of skeletal calcium can be exchanged freely with the extracellular space via the osteoblastic and osteoclastic actions of bone [1, 4]. Forty-eight percent of serum calcium is ionised, and this is its physiologically active state. Forty-six percent is bound to protein, and 7% forms a complex with phosphate, citrate, sulphate, bicarbonate or other anions [1, 2].

Measurement of the plasma calcium is a reflection of the calcium bound to proteins such as albumin and immunoglobulin. The normal range is 2.1–2.6 mmol/L (8.5–10.5 mg/dL) [2]. For every 1 g/dL reduction in the serum albumin, serum calcium decreases by 0.8 mg/dL. Similarly, a 1 g/dL reduction in serum globulin results in serum calcium decreasing by 0.12 mg/dL [1]. While these formulas exist to calculate a corrected calcium level, they have been found to have poor sensitivity and specificity in detecting true hypocalcaemia or hypercalcaemia. Ionised calcium levels are felt to be a more accurate representation of the physiologically active level [2].

In the context of acute metabolic alkalosis, hydrogen ions dissociate from albumin. This subsequently allows albumin to bind more calcium, decreasing the circulating ionised calcium. Ionised calcium levels will fall by 0.12 mg/dL for each change in pH of 0.1 [1].

Extracellular calcium homeostasis is mediated by the gastrointestinal system, kidneys and bone.

2.3.1. Renal handling of calcium

Around 8–10 g of ionised calcium is filtered by the kidneys each day. Of this, around 100–200 mg (2–3% of total filtered calcium) is excreted in the urine [1, 3, 4].

Around 60–70% of calcium is reabsorbed in the proximal convoluted tubule (PCT). This mainly occurs passively via a transepithelial electrochemical gradient established by the reabsorption of sodium and water. A small amount of calcium is reabsorbed by active calcium transport. The process of reabsorption is controlled by PTH and calcitonin [1].

There is no calcium reabsorption in the thin loop of Henle, but a further 20% of calcium is reabsorbed in the thick ascending loop of Henle (TALH). This is predominately mediated by paracellular transport, although some transcellular movement occurs. The apical Na-K-2Cl transporter and the renal outer medullary potassium channel (ROMK) produce a lumen-positive transepithelial gradient for paracellular cation transport, which is caused by a back flux of potassium into the lumen [6, 7]. This consequently causes paracellular calcium reabsorption as demonstrated in **Figure 1** [1, 8]. It also contributes to the reabsorption of other cations such as magnesium and sodium.

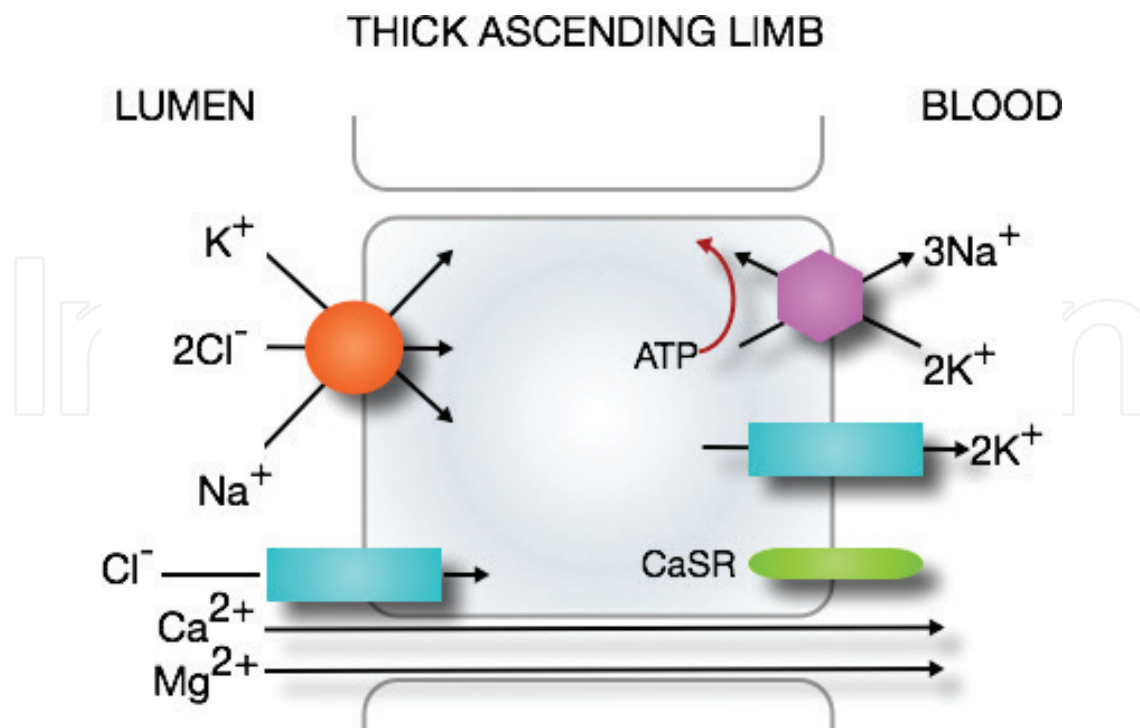


Figure 1. Calcium reabsorption at the thick ascending limb of the loop of Henle. The apical Na-K-2Cl transporter and the renal outer medullary potassium channel are responsible for creating a transepithelial gradient, which drives paracellular calcium transport [1]

The calcium-sensing receptor (CaSR) on the basolateral membrane of the TALH is a G-protein-coupled receptor. It is made up of a large extracellular and cytoplasmic domain [2]. Downregulation of the CaSR increases calcium permeability, while activation impedes permeability. The CaSR inhibits the ROMK channel in the presence of hypercalcaemia, leading to a reduction in paracellular sodium, calcium and magnesium transport [2, 9]. The CaSR enables the ionised calcium level to control renal calcium homeostasis independent of PTH or calcitriol [4].

Claudin-16 and claudin-19 are proteins expressed on the TALH, which facilitate paracellular absorption of divalent cations, including calcium and magnesium [1]. Mutations in claudin-16 are responsible for causing familial hypercalciuria and hypomagnesaemia. Cinacalcet, used for the treatment of secondary hyperparathyroidism in chronic kidney disease, increases claudin-14 mRNA, which subsequently stimulates CaSR activity and decreases paracellular calcium reabsorption [9, 10]. Additionally, PTH and calcitonin upregulate active calcium reabsorption at the TALH [1].

The distal convoluted tubule (DCT) and collecting duct (CD) are responsible for calcium regulation. Around 5–10% of calcium reabsorption occurs through active transport in the DCT, and this mechanism is entirely transcellular [1, 4]. Firstly, calcium travels across the apical membrane by the protein transient receptor potential vanilloid 5 (TRPV5). During this transport process, intracellular calcium is bound to calbindin-D28k and moves towards the basolateral membrane. Finally, calcium reabsorption happens with the help of the sodium-calcium exchanger (NCX1) in conjunction with the plasma membrane calcium ATPase (PMCA1b). This process is represented in **Figure 2** [1, 8].

It is unclear how calcium is transported in the CD; however, a small amount of calcium is thought to be reabsorbed here [2].

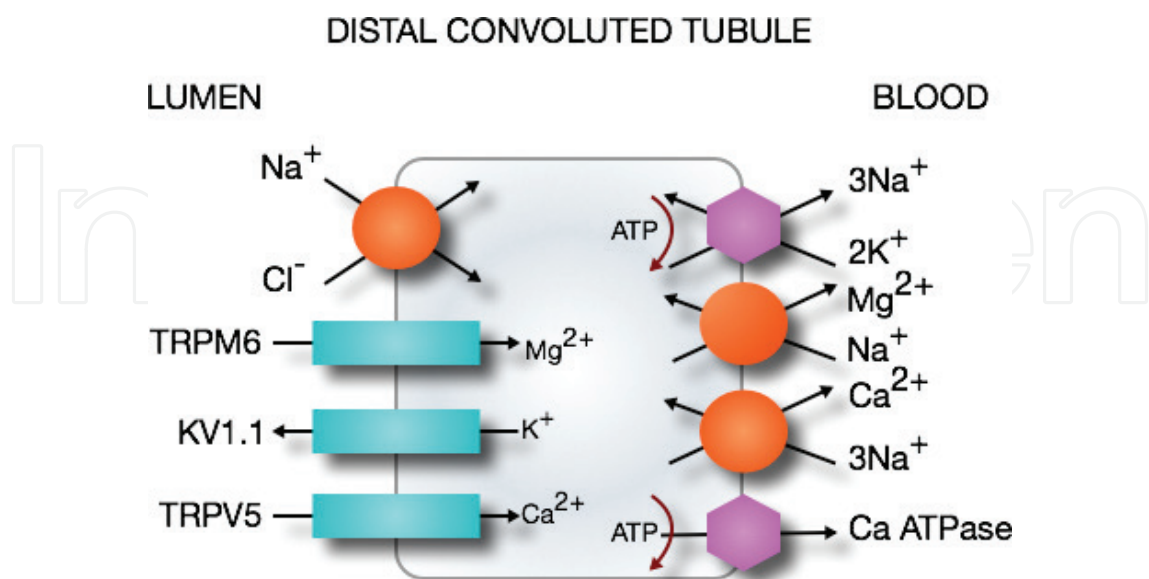


Figure 2. Calcium reabsorption at the distal convoluted tubule. The protein transient receptor potential vanilloid 5 (TRPV5) carries calcium across the apical membrane. Intracellularly calcium binds to calbindin-D28k travelling to the basolateral membrane. The sodium-calcium exchanger (NCX1) and the plasma membrane calcium ATPase reabsorb calcium into the blood [1].

Many mechanisms regulate TRPV5 and therefore renal calcium handling. Mice with absent TRPV5 are known to have hypercalciuria despite normal serum levels of calcium. Their ability to maintain healthy serum calcium levels is believed to be due to increased intestinal absorption mediated by TRPV6 [11]. Calcitriol increases all proteins responsible for transport. Similarly, PTH stimulates TRPV5 and NCX1 while indirectly encouraging calcium reabsorption through the upregulation of calcitriol synthesis. TRPV5, NCX1 and calbindin-D28k are promoted by oestrogen [2].

2.3.2. *Gastrointestinal handling of calcium*

Not all dietary calcium is absorbed as calcium binds with anions (including phosphate and oxalate) in the intestinal lumen to form insoluble salts. Daily intestinal calcium absorption remains relatively constant (200–400 mg per day) despite fluctuations in dietary calcium intake [4, 8].

Gastrointestinal calcium absorption occurs by both transcellular and paracellular mechanisms. The duodenum is the primary site where calcium is absorbed although it also occurs throughout the rest of the small bowel and colon. Transcellular transport is initially mediated by the TRPV6 channel seen on the apical membrane of the duodenum and proximal jejunum [8]. Similar to transcellular absorption in the DCT, once calcium is intracellular, it binds to calbindin, which helps transport the calcium to the basolateral membrane. Here, it is absorbed by calcium ATPase in conjunction with the sodium-calcium exchanger. This is a saturable form of absorption upregulated by calcitriol [2].

In the presence of high luminal calcium concentrations, the passive paracellular pathway of absorption predominates and this is driven by the large concentration gradient between the lumen and cell. This process is nonsaturable. Calcium is bound to the calmodulin-actin-myosin I complex and travels to the basolateral membrane by microvesicular movement [1, 12]. Calcitriol increases calbindin levels and also indirectly influences this process by changing the intracellular tight junction structure [1].

Renal calcium excretion prevents dietary calcium overload, while renal reabsorption and bone resorption compensate for lack of transcellular uptake in the context of low dietary calcium.

2.3.3. *Bone handling of calcium*

Bone acts as a reservoir of calcium stored as hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$). Trabecular bone is 15–25% calcified, while cortical bone is 80–90% calcified. Bone acts as an endocrinological organ by offering a readily exchangeable calcium pool, which is used to maintain calcium homeostasis while also allowing bone modelling and remodelling [2].

At any moment, 15–20% of bone is remodelling, facilitated by osteoblasts and osteoclasts. Osteoblasts are formed from pluripotent mesenchymal stem cells. When activated they assist with osteoclastogenesis, bone matrix production and bone mineralisation [13]. Osteoclasts, derived from circulating myeloid cells, are responsible for bone resorption by disrupting bone matrix mineralisation [2, 13].

Many factors influence bone homeostasis. Receptor activator of NF- κ B ligand (RANKL) promotes osteoclast production. Osteoprotegerin (OPG) is a soluble receptor, which binds to RANKL and,

in doing so, inhibits osteoclast formation. The balance between RANKL and OPG determines the production and function of osteoclasts. PTH activates a PTH receptor (PTH1R) found on osteoblasts. When stimulated, PTH1R upregulates signalling, which favours osteoclast differentiation and bone resorption [13]. The sclerostin/Wnt/beta-catenin pathway also plays a role in controlling bone remodelling whereby sclerostin, which is found in osteocytes, inhibits the Wnt/beta-catenin pathway that works to promote bone formation [2].

2.3.4. *Parathyroid hormone and calcium homeostasis*

PTH is a polypeptide secreted from stored granules in the parathyroid gland. Subsequently, metabolism occurs in the liver and kidney. PTH causes increased plasma calcium levels when hypocalcaemia is detected by CaSRs located on parathyroid cells. It does this by encouraging bone resorption, stimulating intestinal absorption of calcium, upregulating calcitriol production in the kidney (by helping 1- α -hydroxylase that converts vitamin D to calcitriol) and increasing renal calcium reabsorption [1, 2, 4, 8]. PTH is the most significant modulator of calcium reabsorption in the kidney.

PTH secretion is modified by PTH gene transcription, which is upregulated by hypocalcaemia, glucocorticoids and oestrogen. On a post-transcriptional level, PTH is released in reaction to hypocalcaemia, adrenergic agonists, dopamine and prostaglandins [1]. Hypercalcaemia stimulates intracellular destruction of PTH. Calcitriol inhibits PTH gene transcription by binding to the vitamin D receptor element (VDRE) on the PTH gene [2].

2.3.5. *Parathyroid hormone-related peptide and calcium homeostasis*

The discovery of parathyroid hormone-related peptide (PTHrP) was made when investigating the association between malignancy and hypercalcaemia [14]. Many cells produce PTHrP, which has a similar function and structure to PTH and subsequently activates the same receptor as PTH. It is essential endochondral bone formation, smooth muscle relaxation and cellular proliferation and differentiation; however, it appears to have a limited role in calcium homeostasis in healthy adults [4, 15].

PTHrP is known to be released by both solid organ and haematological malignancies, particularly squamous cell carcinoma. It results in a paraneoplastic hypercalcaemia as it binds to the PTH/PTHrP receptor causing calcium resorption from bone and renal calcium reabsorption. PTHrP-mediated hypercalcaemia is a poor prognostic marker in an individual with a malignancy [16].

2.3.6. *Cholecalciferol, calcitriol and calcium homeostasis*

The fat-soluble steroid vitamin D3 (cholecalciferol) is found in the diet and synthesised from 7-dehydrocholesterol under the influence of ultraviolet (UV) light. Subsequently, it undergoes hydroxylation by the hepatic enzyme 25-hydroxylase, resulting in 25-hydroxyvitamin D (calcidiol). Calcidiol circulates bound to vitamin D-binding protein where tubular cells that release 1- α -hydroxylase and 24- α -hydroxylase convert calcidiol to 1,25-dihydroxycholecalciferol (calcitriol) and 24,25-dihydroxycholecalciferol. 24,25-Dihydroxycholecalciferol is an inactive metabolite of vitamin D3 [1, 2, 8, 17]. This process is depicted in **Figure 3**.

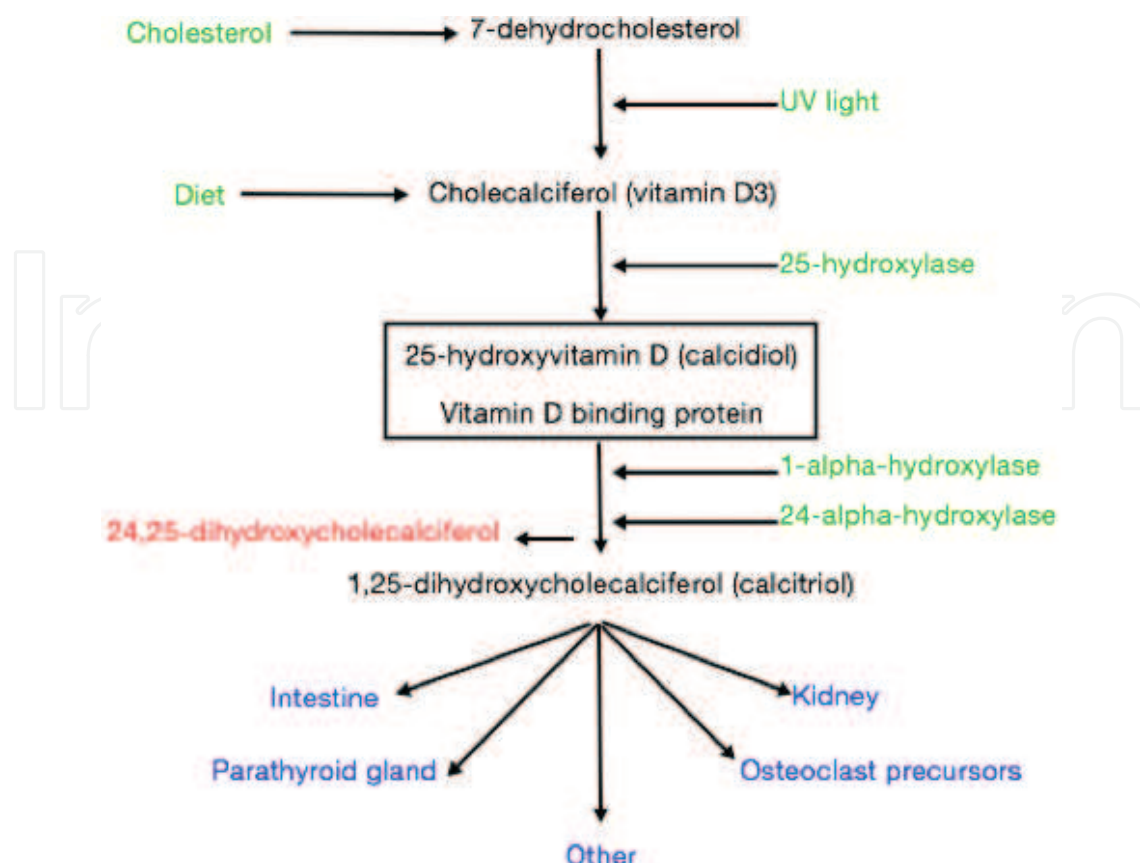


Figure 3. Overview of the metabolism of calcitriol (1,25(OH)₂D). Vitamin D₃ (cholecalciferol) is synthesised from 7-dehydrocholesterol in the presence of UV light and is present in the diet (along with vitamin D₂). It is hydroxylated by the hepatic enzyme 25-hydroxylase resulting in 25-hydroxyvitamin D (calcidiol). Calcidiol circulates bound to vitamin D binding protein. Tubular cells release 1- α -hydroxylase (CYP27B1) and 24- α -hydroxylase, which convert calcidiol to 1,25-dihydroxycholecalciferol (calcitriol) and 24,25-dihydroxycholecalciferol.

Calcitriol increases renal reabsorption of calcium and intestinal absorption of calcium and phosphate, increases the mineralisation of bone and reduces PTH synthesis.

2.3.7. Fibroblast growth factor 23, klotho and calcium homeostasis

Fibroblast growth factor 23 (FGF23) is comprised of 251 amino acids and is produced by osteocytes during bone remodelling. Klotho, expressed in the kidney, parathyroid gland, skeletal muscle and choroid plexus, is a coreceptor for FGF23. Klotho upregulates the affinity of FGF23 to its receptors [18]. FGF23 production causes reduction in calcitriol levels as it blocks 1- α -hydroxylase in the kidney causing increased 24-hydroxylase, which, in turn, causes vitamin D degradation. Additionally, it inhibits PTH release. PTH and hypercalcaemia stimulate FGF23, whereas calcitriol and hypocalcaemia impede its production [19].

FGF23 and klotho also play an important role in phosphate homeostasis, which will be discussed later in the chapter.

2.4. Hypercalcaemia

Hypercalcaemia is a result of disrupted calcium homeostasis and can be caused by alterations to organs, hormones or transporters involved in calcium regulation.

Increased intestinal absorption can be secondary to increased calcium intake, as seen in milk-alkali syndrome, or calcium supplementation [20]. Elevated calcitriol can be seen in primary hyperparathyroidism, T cell lymphomas and vitamin D intoxication. Granulomatous diseases (sarcoidosis, tuberculosis) also cause a rise in calcitriol due to autonomous 1- α -hydroxylase activity in macrophages within granulomas. Increased levels of calcitriol stimulate intestinal absorption of calcium as well as renal calcium reabsorption. Hyperparathyroidism, increased PTHrP, bony metastases, myeloma, phosphate depletion, immobilisation and metabolic acidosis lead to increased bone resorption, which may result in hypercalcaemia. Inability to produce bone, as seen in adynamic bone disease, can also lead to hypercalcaemia. Finally, high calcium levels can be a result of decreased renal excretion of calcium due to volume depletion, thiazide diuretic use or alkalosis [3].

Familial hypocalciuric hypercalcaemia is an autosomal dominant condition caused by a mutation, resulting in loss of function in the CaSR gene. It creates hypocalciuria in the setting of hypercalcaemia, associated with hypophosphataemia, hyperchloraemia and hypermagnesaemia. Patients are mostly asymptomatic although severe hyperparathyroidism can occur in affected neonates [21].

2.4.1. Clinical manifestations of hypercalcaemia

Patients with hypercalcaemia can be asymptomatic at time of presentation or can present with any or all of the following: fatigue, mood changes, confusion, nausea, vomiting, loss of appetite, constipation, polyuria, and weakness. Symptoms are seen more often once calcium levels are greater than 2.9 mmol/L (11.6 mg/dL) or in the setting of acute changes to serum calcium levels. Hypercalcaemia can cause cardiac conduction defects including a short QT interval, which may potentiate a cardiac arrhythmia. Renal tubular damage and calcification involving the vasculature, kidneys, skin, lungs, heart and stomach may follow, especially in the setting of normophosphataemia or hyperphosphataemia. Calcium levels above 3.7 mmol/L (14.8 mg/dL) can result in a comatose state or a cardiac arrest. Renal calculi are associated with chronic hypercalcaemia [4, 22].

2.4.2. Treatment of hypercalcaemia

It is essential to consider and treat the underlying aetiology when managing hypercalcaemia. Treatment approaches depend on the severity and symptomatology of the patient. For mild hypercalcaemia (few symptoms or calcium of <3 mmol/L (<12 mg/dL)), treatment with supportive measures while addressing the underlying disease is appropriate. Intravenous fluids can be used to restore euvolaemia in order to reduce PCT calcium reabsorption and enhance calcium excretion. Avoiding calcium-containing medications and maintaining a low calcium diet is necessary for ongoing management [22].

In those with significant symptoms or calcium levels >3 mmol/L (>12 mg/L), more aggressive therapy is warranted. Intravenous fluids remain the first step in treatment, and the rate of administration is mainly governed by the degree of hypercalcaemia. Fluid administration is thought to lower serum calcium levels by 0.5 mmol/L (2 mg/dL). Loop diuretics can be used once the volume state is restored to prevent renal calcium reabsorption. However, with the

introduction of bisphosphonate therapy for the management of hypercalcaemia, loop diuretics are less frequently utilised unless the patient is suffering from hypervolaemia, oliguric renal failure or congestive cardiac failure [22].

Calcitonin, produced by parafollicular C cells in the thyroid, is effective in lowering serum calcium quickly in cases of severe hypercalcaemia. It acts by blocking osteoclasts and promoting calciuria. Unlike bisphosphonates and steroids, calcitonin works within 4–6 hours; however its effect only lasts for 48–72 hours, because of rapid development of tachyphylaxis, and therefore, it requires administration in conjunction with a longer-acting treatment strategy [22].

Bisphosphonates (particularly, intravenous pamidronate and zoledronate) are used for malignancy-related hypercalcaemia as they inhibit osteoclast action and, therefore, bone resorption. They take 24–48 hours to work. Dose and infusion rate needs to be adjusted to the patient's renal function [23], and risks of treatment include jaw osteonecrosis, uveitis and nephrotoxicity. Denosumab, an antibody against RANKL, has also been used for the treatment of hypercalcaemia of malignancy and has proven effective in bisphosphonate-resistant disease [24].

In calcitriol-mediated hypercalcaemia (e.g., sarcoidosis, tuberculosis), corticosteroids, in conjunction with a low calcium diet, are adequate. Steroids work by inhibiting 1- α -hydroxylase so that calcidiol is unable to be converted to calcitriol.

In those with a parathyroid adenoma causing primary hyperparathyroidism and resultant hypercalcaemia, surgical removal of the adenoma is necessary.

Due to the availability of bisphosphonates, the need for dialysis in hypercalcaemia has been reduced, but it continues to play a role in individuals with oliguric acute kidney injury, life-threatening manifestations of hypercalcaemia or states refractory to other treatment strategies [4].

2.5. Hypocalcaemia

As previously discussed, PTH is essential in maintaining calcium homeostasis, and in hypoparathyroidism (hereditary or acquired), the absence of PTH means that serum calcium levels are unable to be preserved. Severe hypomagnesaemia (<0.4 mmol/L or <0.8 meq/L) can cause hypocalcaemia as it paradoxically impairs PTH release and causes PTH resistance [4]. Dietary deficiency, anticonvulsant therapy, malabsorption, hepatobiliary disease, renal failure and lack of sunlight cause vitamin D deficiency, leading to hypocalcaemia. Drastic reductions in extracellular calcium levels, seen in pancreatitis, severe acute hyperphosphataemia and rhabdomyolysis, lead to hypocalcaemia as PTH is unable to compensate quickly enough to maintain homeostasis.

2.5.1. Clinical manifestations of hypocalcaemia

The level of calcium and the rate of change will determine the manifestation of symptoms in hypocalcaemia. Common symptoms of hypocalcaemia include fatigue, weakness, irritability, confusion and mood changes. Pathognomonic signs of hypocalcaemia are Trousseau's sign (carpopedal spasm occurs when a blood pressure cuff inflated above the systolic blood pressure) and Chvostek's sign (facial muscle spasm following tapping over the facial nerve) [25]. These

signs occur due to neuromuscular excitability [26]. Individuals can also complain of lip paraesthesia, cramping and may experience laryngospasm, bronchospasm, frank tetany or seizures. Cardiac arrhythmias can also occur as low calcium can cause a prolonged QT interval. Chronic hypocalcaemia is associated with cataracts, brittle nails, dry skin and reduced body hair [21].

2.5.2. Treatment of hypocalcaemia

Hypocalcaemia is potentially life-threatening, and any individual experiencing laryngospasm, bronchospasm or seizures should be treated immediately with intravenous calcium. Calcium gluconate can be given peripherally as it causes less local irritation than calcium chloride, which requires administration by central venous access [27]. Patients receiving intravenous calcium should be cardiac monitored as rapid correction can also precipitate arrhythmias [26]. Hypomagnesaemia associated with hypocalcaemia requires treatment with intravenous magnesium initially, followed by calcium correction. Less acute presentations of hypocalcaemia can be treated with oral calcium supplementation (e.g., calcitriol). The daily replacement dose can be between 2 and 4 g of elemental calcium.

Treatment of the underlying cause of hypocalcaemia is essential. In cases of hypocalcaemia due to hypoparathyroidism, treatment with calcium leads to increased calciuresis, which may result in nephrocalcinosis and renal impairment. To reduce calciuresis, thiazide diuretics can be used in association with reduced salt and increased fluid intake. Regular monitoring of serum calcium levels is required.

3. Phosphate

3.1. The importance of phosphate

Phosphate plays a role in skeletal integrity, skeletal development, cell structure, cellular signalling, protein synthesis and energy metabolism [28]. Eighty-five percent of biological phosphorus is stored in the bone, while 15% is found in soft tissue. The remaining phosphate (<1%) circulates in the extracellular fluid [29].

Similar to calcium homeostasis, phosphate balance relies on a complex relationship between the intestine, kidneys, bone, as well as regulatory hormones including PTH, FGF23 and klotho.

3.2. Dietary phosphorus

Humans consume between 700 and 2000 mg of dietary phosphorus each day. Phosphorus is present in dairy and protein-rich foods including meat and poultry. It is frequently added to salt and processed foods. With the increase in consumption of processed foods, average dietary intake has increased [30]. In the human body, phosphorus is present in the form of phosphate [1].

3.3. Physiology of phosphate

The majority, 85%, of phosphate in the body exists as bone. The remaining balance of phosphate is present as free anions or forms organophosphate compounds. Organophosphate

compounds act as structural proteins, enzymes, transcriptional factors, nucleic acids, energy (adenosine triphosphate, creatine phosphate), carbohydrates and lipids [4].

Normal serum phosphate levels in adults range between 0.75 and 1.45 mmol/L (2.5–4.5 mg/dL). Serum phosphate levels do not always reflect available phosphate levels given that phosphate moves freely between the extracellular and intracellular compartments [4].

3.3.1. Renal handling of phosphate

Regulation of renal phosphate reabsorption is felt to be the most critical mechanism in phosphate homeostasis [8, 29]. Each day, 4–6 g of phosphate is filtered by glomeruli.

Eighty-five percent of phosphate undergoes reabsorption at the PCT. This occurs via the type II sodium-phosphate cotransporters Npt2a (SLC34A1) and Npt2c (SLC34A3) located on the brush border of the apical membrane [28, 31]. These cotransporters are endocytosed, favouring phosphaturia, in the presence of PTH, high dietary phosphorus or FGF23. They have a rapid response to changes in the PTH level, with the number of cotransporters adjusting within minutes. It takes approximately 2 hours for the number of cotransporters to change based on dietary phosphorus intake [28]. Npt2c is thought to have less of an influence on phosphate homeostasis in mice as Npt2a knockout mice continue to have profound phosphaturia despite the presence of Npt2c. However, this cotransporter may play a more significant role in human phosphate homeostasis [28]. In humans, mutations in Npt2c lead to hereditary hypophosphataemic rickets with hypercalciuria (HHRH) compared with mutations in Npt2a, which are characterised by the development of nephrocalcinosis and increased osteoporotic risk. These findings support the importance of the Npt2c cotransporter in human phosphate balance [28, 32, 33].

The type III sodium-phosphate cotransporter, PiT2, has been located in the kidney, also at the brush border membrane. This transporter is upregulated by low dietary phosphate, albeit more slowly than the type II sodium-phosphate cotransporters, with changes in concentrations taking 8 hours [28].

Npt2a and 2c are responsible for transporting divalent phosphate with Npt2a, moving three sodium ions and one phosphate ion across the apical membrane creating an electrogenic gradient. Npt2c transports two sodium and one phosphate ion, resulting in electroneutrality. PiT2 carries monovalent phosphate, also developing an electrogradient [1]. An unknown transporter on the basolateral membrane is thought to be responsible for phosphate transport to peritubular capillaries. This is represented in **Figure 4**.

Hypocalcaemia, hypomagnesaemia, hypophosphataemia and dehydration inhibit reabsorption of phosphate at the kidney. Fluid overload upregulates phosphate excretion [4].

3.3.2. Intestinal handling of phosphate

Different species display diverse mechanisms for intestinal absorption of phosphate, and therefore the understanding of human intestinal phosphate handling is incomplete [34].

Intestinal phosphate absorption occurs via passive paracellular and active transcellular transport. In healthy humans, 60–75% of dietary phosphorus is absorbed [4, 21]. Paracellular transport involves passive diffusion of phosphate through tight junctions and occurs independently

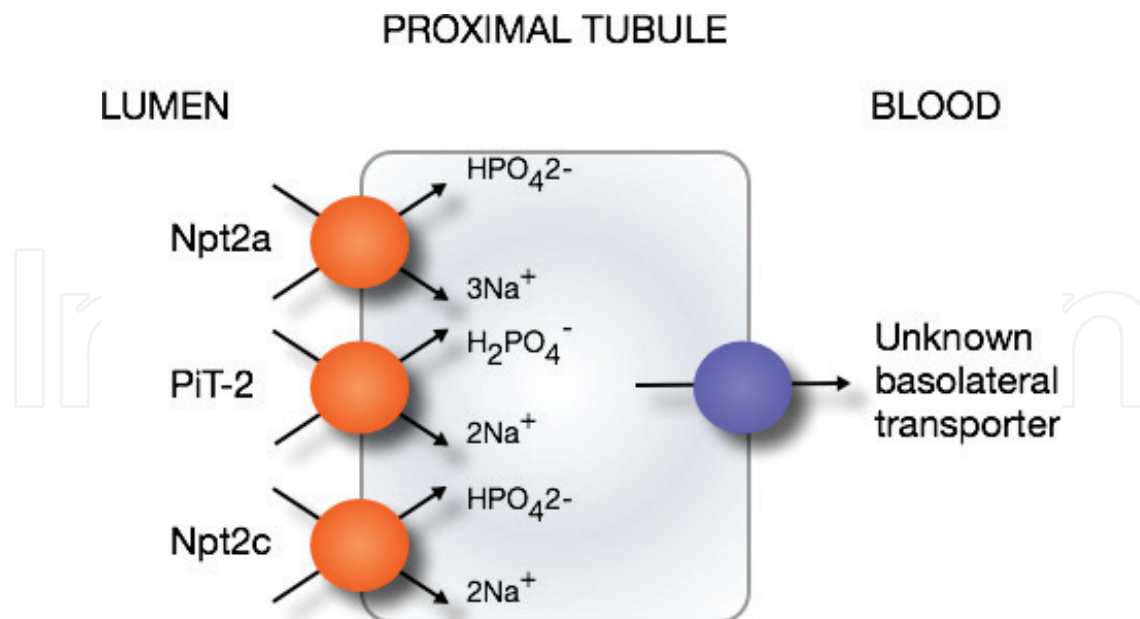


Figure 4. Sodium-phosphate cotransporters at the proximal convoluted tubule. Npt2a, Npt2c and PiT2 are located on the brush border of the apical membrane. Npt2a and 2c transport divalent phosphate. Npt2a transports three sodium ions with one phosphate ion, creating an electrogenic gradient. Npt2c moves two sodium ions for one phosphate, which is electroneutral. PiT2 carries monovalent phosphate creating an electrogradient. An unknown transporter on the basolateral membrane transports phosphate to peritubular capillaries [1].

of any regulatory hormones [34]. The type II sodium-phosphate cotransporter, Npt2b (SLC34A2), and type III cotransporters, PiT1 and PiT2, modulate transcellular transport in the intestine. Npt2b is located on the apical membrane of enterocytes and is thought to be most abundant in the duodenum and jejunum in humans [1] although it is also found on lung, mammary, liver, and testis tissue [31, 34]. Mutations in Npt2b transporters do not manifest in clinically significant hypophosphataemia in humans, and this is thought to be due to renal compensation [28]. The type III cotransporters are predominately present on the basolateral intestinal membrane but can be found on the apical membrane [35].

Gastrointestinal absorption of phosphate is primarily upregulated by calcitriol and low dietary phosphate. FGF23 reduces the abundance and activity of sodium-phosphate cotransporters and will be discussed further in this chapter. Matrix extracellular phosphoglycoprotein (MEPE) produced by osteoblasts and osteocytes inhibits renal and intestinal phosphate absorption independent of PTH and FGF23 [34]. Other regulators of phosphate absorption are glucocorticoids, oestrogen and the presence of metabolic acidosis [28]. Calcium salts, sevelamer hydrochloride and aluminium hydroxide prevent intestinal absorption of phosphate and are therefore used as phosphate binders in patients with chronic kidney disease [4].

3.3.3. Bone handling of phosphate

Similar to calcium, bone acts as a reservoir of phosphate. Phosphate can be resorbed from bone into the extracellular space to maintain serum levels of phosphate.

3.3.4. *Fibroblast growth factor 23, klotho and phosphate homeostasis*

FGF23 is the most widely studied phosphatonin and acts with its coreceptor, klotho. Dietary phosphorus and calcitriol increase the secretion of FGF23, which encourages phosphaturia through reduced Npt2a expression in the PCT. It plays a similar role in downregulating Npt2c and PiT2; however, in mice studies, this effect has been less pronounced [36]. Conversely, low dietary phosphorus inhibits FGF23 secretion.

FGF23 also contributes to phosphate homeostasis by regulating the number of intestinal sodium-phosphate cotransporters [1]. Similar to the kidney, cotransporters are less abundant in the presence of high levels of FGF23, preventing absorption of phosphorus.

Animal and in vitro studies have proved that FGF23 works directly on the parathyroid gland to decrease PTH production and release [37]. In chronic kidney disease, the parathyroid becomes increasingly resistant to the action of FGF23, contributing to the development of secondary and tertiary hyperparathyroidism [1]. As previously stated, FGF23 also inhibits calcitriol, preventing intestinal phosphate absorption and renal reabsorption [19].

3.3.5. *PTH and phosphate homeostasis*

PTH reduces the number of sodium-phosphate cotransporters, specifically Npt2a, in the kidney favouring phosphaturia [32, 37]. Serum phosphate levels have a direct effect on the parathyroid gland independent of calcitriol, calcium levels or FGF23. This is mediated by modulation of PTH gene expression and parathyroid cell proliferation [37] but requires intact and functioning parathyroid tissue [38].

3.4. Hyperphosphataemia

Hyperphosphataemia is most often associated with impairment in the kidney's ability to excrete appropriate levels of phosphate [37]. Acute kidney injury leads to hyperphosphataemia due to a reduction in glomerular filtration rate [21]. In early chronic kidney disease, increased phosphate levels are compensated for by FGF23 initially, followed by PTH. With time and a further decrease in glomerular filtration (specifically, at less than an eGFR of 35 mL/min/1.73²), these mechanisms are unable to accommodate due to loss of renal mass meaning that phosphate levels rise. Impaired calcitriol synthesis and bone mineralisation also contribute to elevated phosphate levels. Hyperphosphataemia drives secondary hyperparathyroidism and increased FGF23, which is common in patients with end-stage kidney disease [29]. FGF23 suppresses calcitriol with resultant adverse effects on cardiovascular and kidney health.

Other causes for hyperphosphataemia are driven by elevated exogenous phosphate, as seen following administration of phosphate enemas or excess endogenous phosphate. Bisphosphonate treatment can cause elevated phosphate levels due to the liberation of phosphate from bone. Rapid release of intracellular phosphate into the extracellular space is seen in rhabdomyolysis, tumour lysis syndrome and acidosis [29, 39]. As PTH has a significant influence on promoting phosphaturia, loss of PTH caused by hypoparathyroidism or peripheral resistance to its action (pseudohypoparathyroidism) can produce elevated phosphate levels

[21]. Familial tumoral calcinosis, an autosomal recessive disease caused by a mutation in the GALNT3, FGF23 or klotho gene, is characterised by resistance to FGF23, which also leads to hyperphosphataemia [40]. Increased levels of growth hormone and insulin-like growth factor 1 (Igf-1) seen in acromegaly stimulate phosphate reabsorption in the PCT.

3.4.1. Clinical manifestations of hyperphosphataemia

Acute hyperphosphataemia results in soft tissue calcium and phosphate deposition contributing to hypocalcaemia. These individuals may present with manifestations of hypocalcaemia or with consequences of calcium phosphate deposition including nephrocalcinosis or heart block [4]. Chronic elevation in phosphate levels can lead to vascular calcification, mineral bone disease, secondary hyperparathyroidism and calciphylaxis.

Elevated phosphate levels in patients requiring haemodialysis for end-stage kidney disease is associated with an increased risk of cardiovascular morbidity and mortality [41, 42].

Elevated FGF23 levels, seen in individuals with hyperphosphataemia, have been found to contribute to left ventricular hypertrophy, reduced erythropoiesis and increased inflammation [36].

3.4.2. Treatment of hyperphosphataemia

Acute hyperphosphataemia is managed with intravenous fluids, renal replacement therapy and treatment of the underlying cause [21].

Management of hyperphosphataemia remains a challenge in patients with chronic kidney disease. Low phosphate diets, phosphate binders and dialysis are all used as treatment strategies to maintain healthy phosphate levels. Intensive dialysis (daily or nocturnal dialysis) has been shown to decrease the requirement for phosphate binders and dietary restriction [43].

3.5. Hypophosphataemia

Hypophosphataemia can be caused by impaired phosphate absorption, increased phosphate loss or movement of phosphate from the extracellular space. Reduced phosphate consumption is rare but seen in individuals who are not eating and in those who abuse alcohol. Hypophosphataemia is a known consequence of refeeding syndrome. Primary hyperparathyroidism often presents with mild hypercalcaemia and hypophosphataemia.

Inherited disorders including autosomal dominant, autosomal recessive or X-linked hypophosphataemic rickets and vitamin D-dependent rickets cause excess phosphate loss associated with skeletal deformities. Primary hyperparathyroidism encourages downregulation of NPT2a, resulting in phosphaturia. Proximal tubular dysfunction occurs in proximal tubular acidosis or Fanconi syndrome and contributes to phosphate loss. Hypophosphataemia is common following renal transplantation and is thought to be secondary to persistently elevated FGF23 levels [21].

Causes of intracellular redistribution of phosphate include diabetic ketoacidosis, acute respiratory alkalosis, likely due to muscular sequestration of extracellular phosphate (chronic

respiratory alkalosis leads to hyperphosphataemia) and insulin therapy. If phosphate is omitted from TPN, it can cause reductions in serum phosphate. Rarely, mesenchymal tumours such as haemangiopericytomas, fibromas and angiosarcomas can secrete phosphatonins such as FGF23. Subsequently, this results in phosphaturia and hypophosphataemia.

3.5.1. Clinical manifestations of hypophosphataemia

Hypophosphataemia does not cause clinical sequelae until levels are less than 0.65 mmol/L (2 mg/dL). Muscle weakness, including diaphragmatic weakness and reduced cardiac contractility, can be a consequence of hypophosphataemia. Other manifestations include osteomalacia, metabolic encephalopathy, haemolysis, leukocyte dysfunction and thrombocytopenia [4, 21, 42].

3.5.2. Treatment of hypophosphataemia

Dairy intake or oral phosphate supplementation can treat hypophosphataemia, except in cases of nephrocalcinosis or nephrolithiasis due to urinary phosphate wasting. In the case of severe hypophosphataemia, intravenous replacement should be given. In individuals requiring parenteral nutrition, phosphate needs to be added to any nutritional supplement.

4. Magnesium

4.1. The importance of magnesium

The divalent cation magnesium plays an integral role in neuromuscular activity. On an intracellular level, it is the second most abundant cation [21]. It is essential to the activation of adenosine triphosphate (ATP), intracellular signalling, glycolysis, protein formation, cell growth as well as DNA production and transcription [44]. Given its function at the cellular level, it is essential in the role of many human organs including the heart, vasculature, muscle, bone and central and peripheral nervous systems [44].

The normal plasma level of magnesium is 0.7–1.1 mmol/L (1.7–2.6 mg/dL). Similar to calcium and phosphate homeostasis, the kidney, intestine and bone are essential in maintaining its balance.

4.2. Dietary magnesium

The average daily consumption of magnesium from the diet is 140–360 mg. Many foods including fruits, vegetables, cereals, grains, nuts and legumes contain magnesium [45]. Processed, refined and boiled foods are low in magnesium as are dairy products [44, 45].

4.3. Physiology of magnesium

Around 20–28 g of magnesium is present in an average-sized adult with more than half of this being stored in bone [4, 45]. The remaining magnesium is distributed in muscle and soft

tissue, and 1% is found in the extracellular compartment [1, 4, 44]. About 30% of magnesium is bound to protein, including albumin, with 10% bound to ATP, nucleic acids, and phospholipids [1]. The remaining 60% exists in the ionised state; it is physiologically active in this form.

Many essential functions in the human body require magnesium; however, it does not appear that hormones have a significant influence on its balance. The kidney, intestine and bone are primarily responsible for maintaining healthy magnesium levels.

4.3.1. Renal handling of magnesium

Under normal physiological conditions, 2000–2400 mg of magnesium is filtered by the kidney each day. Around 10–20% of filtered magnesium undergoes reabsorption by the PCT. This occurs through a predominately paracellular pathway driven by a transepithelial electrochemical gradient caused by sodium reabsorption [46]. In the TALH, 50–70% of magnesium is reabsorbed, also via a paracellular pathway. A lumen-positive transepithelial gradient driven by NKCC2 and ROMK is required. Loop diuretics inhibit the NKCC2 transporter, resulting in magnesium excretion. Claudin-16 and claudin-19 affect the tight junction permeability at the TALH, also altering magnesium reabsorption [46]. The DCT reabsorbs the remaining 10–15% of magnesium. Here, reabsorption occurs through a transcellular pathway mediated by TRPM6, which is present on the apical surface [46, 47]. Epidermal growth factor (EGF) [48] and the sodium-potassium-ATPase transporter increase TRPM6 and therefore the transport of magnesium. The magnesium-sodium exchanger (SLC41A1) on the basolateral membrane facilitates reabsorption into the peritubular capillaries [49].

Renal magnesium reabsorption is thought to be upregulated by PTH but inhibited by hypermagnesaemia and hypercalcaemia [4].

4.3.2. Gastrointestinal handling of magnesium

Intestinal absorption of magnesium depends on dietary intake, but approximately 40% is absorbed. In humans, this predominately takes place in the jejunum and ileum with a small amount being reabsorbed in the colon [44, 50].

Saturable, transcellular magnesium absorption occurs through TRMP6 and TRMP7 channels [1, 44, 47]. Thirty percent of intestinal magnesium absorption occurs through the transcellular mechanism; however, this increases in the instance of low dietary magnesium intake. In cases of high luminal magnesium, the paracellular route predominately drives transport and accounts for 80–90% of intestinal magnesium uptake.

4.3.3. Bone handling of magnesium

Around 50–60% of bodily magnesium is stored in the bone as hydroxyapatite crystals [46]. Half of this is insoluble with the remainder being freely exchangeable with the extracellular fluid. Magnesium has been found to encourage osteoblast differentiation and proliferation, resulting in reduced bone formation in hypomagnesaemic individuals [51].

4.4. Hypermagnesaemia

Exogenous magnesium is found in oral and intravenous magnesium supplementation, rectal enemas, antacids, laxatives and urethral irrigation solutions [45]. Elevated magnesium levels are seen in patients given exogenous magnesium in the context of renal insufficiency but can occur in the presence of normal renal function [21, 45]. The release of intracellular magnesium into the extracellular space is seen in individuals with severe burns, trauma or shock. Associations with hypermagnesaemia include familial hypocalciuric hypercalcaemia, adrenal insufficiency, hypothyroidism and hypothermia.

4.4.1. Clinical manifestations of hypermagnesaemia

Clinical sequelae caused by hypermagnesaemia can occur with levels greater than 2 mmol/L (4.8 mg/dL). Hypermagnesaemia can cause hypotension as a result of vasodilation. Other manifestations include nausea, vomiting, fatigue, neurological impairment and potentially paralysis. Deep tendon reflexes are lost when serum magnesium is greater than 3 mmol/L. Reduced bowel sounds, facial flushing, dilated pupils and heart block are clinical signs, which may manifest [1, 4].

4.4.2. Treatment of hypermagnesaemia

Hypermagnesaemia requires management by ceasing exogenous magnesium administration. Intravenous hydration and intravenous calcium can be used in symptomatic individuals. Calcium is thought to antagonise the effects of magnesium at the neuromuscular junction. Renal replacement therapy is an option in those with chronic kidney disease.

4.5. Hypomagnesaemia

Gastrointestinal causes for hypomagnesaemia include inadequate dietary magnesium intake, gastrointestinal loss through vomiting or diarrhoea, malabsorption, small bowel surgery and alcoholism [46, 52]. Primary familial hypomagnesaemia caused by TRPM6 mutations can result in reduced gastrointestinal absorption and renal loss.

Excessive renal magnesium loss at the PCT is seen with the use of frusemide and in Bartter syndrome; although this is usually mild due to distal compensation. Hypercalcaemia leads to hypomagnesaemia due to competition for transport at the TALH and CaSR activation [52]. Familial hypomagnesaemia with hypercalciuria can occur in mutations of claudin-16 and 19 [53]. At the DCT, thiazide diuretics and Gitelman syndrome cause urinary magnesium loss. EGF upregulates TRPM6, and therefore EGF receptor inhibitors (cetuximab, panitumumab) contribute to hypomagnesaemia. Nephrotoxic medication such as aminoglycosides, amphotericin B, cisplatin, calcineurin inhibitors, pentamidine and cyclosporine can cause hypomagnesaemia [4].

In refeeding syndrome, recovery from diabetic ketoacidosis, pancreatitis, bony metastatic disease and post-parathyroidectomy magnesium can shift from the extracellular to intracellular space.

Chronic proton pump inhibitor use has been associated with hypomagnesaemia, particularly with concomitant diuretic use [52, 54]. The mechanism behind this has been thought to be due to reduced gastrointestinal absorption although causality remains under investigation [54].

4.5.1. Clinical manifestations of hypomagnesaemia

Hypomagnesaemia can result in mood changes, fatigue, muscular spasm, weakness and neuromuscular excitability, which may manifest as hyperreflexia, carpopedal spasm, seizures and tremor [46]. Prolonged QT intervals and ST depression resulting in cardiac arrhythmias can occur. Hypomagnesaemia may potentiate digoxin toxicity. Due to urinary losses, hypocalcaemia and hypokalaemia are often seen with hypomagnesaemia [21].

4.5.2. Treatment of hypomagnesaemia

Hypomagnesaemia requires treatment with oral or intravenous replacement. Oral magnesium supplementation is not well absorbed when used in high doses and can cause diarrhoea. Individuals presenting with symptoms or cardiac manifestations should be treated promptly with intravenous magnesium [45].

5. Conclusion

Calcium, phosphate and magnesium are electrolytes found in the human body, which rely on tight regulatory control in order to support human life and function. The kidney, intestine and bone are essential in maintaining the fine balance. Diseases affecting any of these organs, or the hormones involved in homeostasis, can disrupt the levels of each electrolyte causing symptomatic and potentially life-threatening consequences.

In addition to the kidney, intestine and bone, calcium relies on PTH, PTHrP, phosphate, cholecalciferol, calcitriol, FGF23 and klotho to maintain normal serum levels in the human body. Individuals with hypercalcaemia and hypocalcaemia can present with asymptomatic or symptomatic disease depending on the severity and chronicity. It is important to manage each condition to prevent immediate and long-term complications.

Phosphate and calcium are dependent on each other with disruption to the balance of one having impacts on the other. Phosphate homeostasis is also reliant on PTH, FGF23 and klotho. Hyperphosphataemia is common in patients with chronic kidney disease and has many long-term ramifications, and hypophosphataemia can lead to severe illness and death.

Magnesium does not appear to rely on hormonal control. It plays important roles in neuromuscular activity. Hypermagnesaemia is rare in cases of normal renal function and is most often a result of exogenous ingestion. Hypomagnesaemia may be due to a wide array of causes and disturbs neuromuscular signalling.

Clinicians require a thorough understanding of the intricacies of calcium, phosphate and magnesium homeostasis in order to prevent, diagnose and manage complications of disturbance.

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