Calcium Disorders

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S. Llahana et al. (eds.), *Advanced Practice in Endocrinology Nursing*,
https://doi.org/10.1007/978-3-319-99817-6_51

Abstract

The plasma levels of calcium and inorganic phosphate are controlled by homeostatic mechanisms. The plasma level of calcium is particularly tightly controlled. Parathyroid hormone (PTH) raises calcium via actions on: bone cells (osteoclasts and osteocytes) to promote mineral resorption; the renal distal tubule to enhance calcium reabsorption; and renal proximal tubule cells to promote 1,25-dihydroxyvitamin D synthesis. Calcium-sensing receptors lower calcium dependent on plasma membrane expression in cells of: the parathyroid gland to suppress PTH secretion and thus serum PTH levels; the renal cortical thick ascending limb to promote urinary calcium losses; and other tissues including thyroid calcitonin-secreting C-cells and osteoclasts. Hypocalcaemia arises as a consequence of a failure of one of the normal homeostatic mechanisms that act to raise the plasma calcium level. Hypocalcaemia may be symptomatic or asymptomatic. Key early clinical features of hypocalcaemia include perioral or peripheral paresthesiae or numbness, and various manifestations of neuromuscular excitation including carpo-pedal spasm. Later, more severe manifestations of hypocalcaemia include convulsions, including febrile convulsions in children. Dietary calcium requirements for adults are around 1–1.5 g/day, reflecting relatively low levels of intestinal absorption efficiency, even in vitamin D replete individuals. Calcium supplements are of particular benefit in patients with osteoporosis on anti-resorptive medications, which impair calcium release from bone, thereby promoting the risk of hypocalcaemia. Hypercalcemia arises as a consequence of a failure of one or more of the normal homeostatic mechanisms that act to lower the plasma calcium level.

Keywords

Calcium metabolism · Calcium-sensing receptor · Hypercalcemia · Hypocalcaemia Hypophosphatemia · Parathyroid hormone Phosphate metabolism

Abbreviations

ADH	Autosomal dominant hypocalcaemia
ATP	Adenosine 5′-triphosphate
CaSR	Calcium-sensing receptor
DXA	Dual energy Xray absorptiometry
FGF-23	Fibroblast growth factor-23
FHH	Familial hypocalciuric hypercalcemia
NSHPT	Neonatal severe hyperparathyroidism
PTH	Parathyroid hormone

Key Terms

- **Hydroxyapatite:** is a key bone mineral composed of Calcium and phosphate.
- **Ionized calcium:** is free calcium in blood that is not attached to proteins.
- **Calcium sensing receptor:** regulates calcium metabolism by regulating parathyroid hormone secretion and urinary calcium excretion.
- **Osteomalacia:** an end-stage bone disease of chronic and severe vitamin D or phosphate depletion of any cause.

Key Points

- Bone is composed of collagen protein fibres strengthened by a mineral phase. Calcium and inorganic phosphate are the two key chemical components of bone mineral, also known as crystalline hydroxyapatite.
- Calcium ions via both the extracellular and several intracellular pools are critical for various important cell functions including interactions between key proteins. Inorganic phosphate ions are also critical for normal cell function.
- The metabolisms of calcium and inorganic phosphate are subject to homeostatic control mechanisms. One key element of the control mechanism is parathyroid hormone (PTH) from the parathyroid gland, which elevates the plasma calcium concentration and suppresses the plasma phosphate concentration. The calcium-sensing receptor lowers the plasma calcium concentration by mediating negative feedback control of PTH secretion and promoting urinary calcium excretion.
- Vitamin D exists in several forms in the body, primarily as metabolites of vitamin D_3 (cholecalciferol). 25-Hydroxyvitamin D is the primary circulating form and is used to assess the whole body vitamin D store. 1,25-Hydroxyvitamin D is the active hormonal form, which stimulates calcium absorption from the small intestine and renal distal tubule.
- Disorders of calcium metabolism leading to hypercalcemia or hypocalcaemia arise from disturbances of the homeostatic mechanisms.

51.1 Introduction

Calcium and phosphate are the two main components of the key bone mineral, hydroxyapatite. In addition, the extracellular ionised Ca^{2+} concentration is a key determinant of neuromuscular excitability and is required for coagulation, and control mechanisms that up- or down-regulate the intracellular Ca^{2+} concentration drive or suppress key cell functions including muscle contraction and the secretion of key hormones including insulin and even digestive enzymes. Inorganic phosphate, on the other hand, plays major roles in reactions that are critical for human biochemistry acting, for example, to enable the storage of chemical energy as ATP, facilitate many of the reactions of intermediary metabolism, and shift the activation states of enzymes and proteins via reversible phosphorylation. For these reasons, the plasma levels of both calcium and phosphate are subject to tight regulation. The plasma ionised Ca^{2+} concentration is subject to particularly tight control. In this chapter, we consider the normal plasma levels of both calcium and phosphate as well as causes of disturbances in their levels, focusing in particular on key mechanisms that underlie hyper- and hypocalcaemia.

51.2 Calcium and Phosphorus Metabolism and Testing

51.2.1 Calcium

The normal range for the plasma total calcium concentration in humans is around 2.2–2.6 mmol/L, distributed between three major fractions:

1. One in which calcium is bound to plasma proteins, chiefly albumin (representing around 45%).
2. One taking the form of filterable complexes including calcium citrate (around 5%).
3. A free, ionised fraction (i.e. Ca^{2+} ions; around 50%).

As a result the normal range for plasma ionised Ca^{2+} concentration, which may be measured by a suitable Ca^{2+}-selective electrode, is 1.1–1.3 mmol/L. It is the ionised Ca^{2+} concentration that controls the coagulation cascade and modulates cell and tissue function. For example, low extracellular Ca^{2+} concentration enhances excitability at the neuromuscular junction. Thus, any factor that perturbs the ionised Ca^{2+} concentration can perturb cell function. One important factor is a change in pH leading to a change in Ca^{2+} binding to albumin; an increase in pH increases Ca^{2+} binding to albumin and thereby acutely lowers the ionised Ca^{2+} concentration. A drop in the plasma albumin concentration is typically accompanied by a drop in the total plasma calcium concentration so that the ionised Ca^{2+} concentration does not change.

The ionised Ca^{2+} concentration is protected by several key factors (review: Brown and MacLeod 2001):

1. Ca^{2+} ion sensing by cells of the parathyroid gland to suppress the secretion of a peptide hormone parathyroid hormone (PTH) that promotes calcium transfers into the extracellular fluid and, thus, the blood.
2. Ca^{2+} ion sensing by cells of the thick ascending limb of the renal tubules to suppress Ca^{2+} reabsorption from the tubular fluid.
3. Ca^{2+} ion sensing by parafollicular C-cells of the thyroid to activate the secretion of a peptide hormone, calcitonin that suppresses osteoclastic-dependent bone resorption.
4. Ca^{2+} ion sensing by the proximal tubule to suppress the synthesis of 1,25-dihydroxyvitamin D_3.

51.2.2 Phosphate

The plasma inorganic phosphate concentration lies in the range 0.8–1.4 mmol/L present as the free ion distributed between two main species HPO_4^{2-} and $H_2PO_4^-$, dependent upon the pH. At normal plasma pH 7.40, the ratio of HPO_4^{2-}:$H_2PO_4^-$ is around 5:1. The ratio falls as the pH drops and increases as the pH rises. $CaHPO_4$ is poorly soluble and, as might be expected, the problem is exacerbated at high pH as the concentration of HPO_4^{2-} increases.

Table 51.1 Causes of hypophosphatemia

Primary disturbances of mineral metabolism
1. Acquired
• Primary hyperparathyroidism
• Vitamin D deficiency
2. Inherited
• Autosomal dominant hypophosphatemic rickets (mutant stable form of FGF-23)
• X-linked (dominant) hypophosphatemic rickets (mutant PHEX; defective negative regulation of FGF-23 production)
• X-linked recessive hypophosphatemic rickets (various forms including mutations in renal Na-phosphate co-transporters)
Nutritional causes
• Acute alcoholism
• Refeeding after prolonged under nutrition
• Diabetic ketoacidosis (recovery phase)
Miscellaneous
• Severe burns
• Diuretic use

51.2.3 Disorders of Phosphate Metabolism

Hypophosphatemia is associated with proximal myopathy and cardiomyopathy. It is also associated with various forms of rickets and osteomalacia. Hypophosphatemia arises in some important nutritional disorders. A number of inherited and acquired conditions are also associated with hypophosphatemia (see Table 51.1).

Hyperphosphatemia typically occurs in chronic kidney disease and contributes to vascular mineralisation and associated peripheral, coronary and cerebral vascular disease. In this setting, the plasma calcium level may be low. Hyperphosphatemia also occurs in hypoparathyroidism and parathyroid hormone resistance states (pseudohypoparathyroidism) as well as disorders of FGF-23 metabolism, in which the serum levels of FGF-23 are suppressed and the serum levels of 1,25-dihydroxyvitamin D are elevated (review: Conigrave 2012).

51.3 Dietary Calcium and Calcium Supplementation

Dietary calcium intakes vary considerably dependent on dietary composition. Foods rich in calcium include various dairy products including

Table 51.2 Calcium-rich foods

• Dairy products (including milk, yoghurt, cheese and ice cream)
• Salmon or sardines (containing edible bones)
• Tofu (set with calcium salts)
• Almonds
• Broccoli, cabbage, soy-beans, tahini (sesame seeds), bok-choy, celery
• Dried figs, dried apricots, oranges

whole milk, skim milk, yoghurt and cheese. Some forms of fish, nuts, vegetables and fruit are also rich sources of calcium (see Table 51.2).

Recommended daily allowances of calcium are based on balance studies and suggest that optimal calcium intakes are around 1.0 g/day during childhood and around 1–1.5 g/day during adolescent growth, and during pregnancy and lactation. Lower calcium intakes are required in adult men and in women post-lactation and in the peri- and postmenopausal stages but are still around 1.0 g/day. The relatively high levels of recommended calcium intake reflect, in part, the low efficiency of intestinal calcium absorption, which is around 10–20% even when vitamin D levels are replete (Conigrave 2012).

Until recently, almost all patients, men and women, with osteoporosis have been prescribed both calcium and vitamin D supplements at doses of around 1.0–2.0 g/day and 1000–2000 IU/day, respectively. In the presence of anti-resorptive therapy with one of the oral or intravenous bisphosphonates, subcutaneous denosumab, selective estrogen receptor modulator (SERM) raloxifene or even oestrogen therapy, the benefits of supplementation with calcium and vitamin D are relatively straightforward. They prevent the development of acute symptomatic hypocalcaemia. Hypocalcaemia can develop in this setting as a result of anti-resorptive-induced impairment of osteoclastic bone resorption and the unopposed formation and mineralisation of new bone. In patients taking anti-resorptive therapy, increased intakes of calcium and vitamin D prevent acute hypocalcaemia by increasing the amount of calcium absorbed by the small intestine each day.

In the absence of anti-resorptive therapy, the value of calcium and vitamin D supplements in adults is less certain and benefits in terms of improved bone mineral density and muscle mass and function are at best modest. Two additional circumstances in which calcium and vitamin D supplements should be considered even in the absence of therapy with anti-resorptive agents are:

1. Low serum vitamin D levels (<40 nmol/L). Defining the normal range for serum 25-hydroxyvitamin D_3 in adults has proved difficult. However, the risk of osteomalacia increases markedly at serum concentrations below 30 nmol/L and serum PTH levels are suppressed at serum 25-hydroxyvitamin D_3 levels up to 80 nmol/L.
2. Evidence of secondary hyperparathyroidism and high bone turnover (high serum PTH in the presence of a low plasma calcium concentration with elevated bone turnover markers including the pro-collagen breakdown product P1NP and ostase reporting bone formation and the plasma CTX and urinary level of deoxypyridinoline cross-links reporting bone resorption).

51.4 Hypocalcaemia

51.4.1 Diagnosis of Hypocalcaemia

Two main sources of information are: (1) the plasma calcium levels reported by the biochemistry laboratory and (2) the patient's clinical state. The former requires careful consideration of key related information including the plasma albumin concentration and plasma pH. The latter can be somewhat unpredictable: patients who experience a relatively small but acute drop in plasma calcium concentration can be symptomatic and exhibit many of the clinical features of hypocalcaemia. On the other hand, patients with long-standing moderate-severe hypocalcaemia can be asymptomatic or only mildly symptomatic and display only modest clinical features indicating that appropriate physiological adjustments are made in the presence of persistently low calcium levels (Brown and MacLeod 2001).

The clinical features of hypocalcaemia include enhanced neuromuscular excitability including fasciculations and tetanic contractions of isolated muscle groups, which may be either spontaneous or elicited by tapping directly over nerves, e.g. the facial nerve at the angle of the mandible

(Chvostek's sign), or by inflating a blood pressure cuff to a level above the systolic pressure for 2–3 min to induce local hypoxemia (Trousseau's sign). Other clinical features include perioral or peripheral numbness, bronchospasm and even convulsions.

51.4.2 Laboratory Contribution to Diagnosis of Hypocalcaemia

As noted above, hypocalcaemia is defined by two ranges: one for plasma total calcium concentration (2.2–2.6 mmol/L) and one for plasma ionised Ca^{2+} concentration (1.1–1.3 mmol/L). In terms of pathophysiological significance, a low ionised Ca^{2+} concentration is more important but assays for ionised Ca^{2+} are not always available. In the presence of hypoalbuminemia (e.g. in the context of uncompensated chronic liver disease), the plasma ionised Ca^{2+} concentration is frequently normal despite the presence of a low plasma total calcium concentration. This arises from a significant reduction in the plasma protein calcium binding capacity. To confirm that the plasma calcium concentration is normal in this setting either (1) the plasma ionised Ca^{2+} concentration can be measured and/or (2) a correction can be made to the total calcium concentration using an appropriate formula (Payne et al. 1973).

An example of such a formula is as follows:

$$\text{Plasma total Ca}\left(\text{corrected; mmol / L}\right) = \text{plasma total Ca}\left(\text{measured; mmol / L}\right) + [0.025\ \text{mmol / g} \times \left(40\text{g / L}^{*} - \text{plasma albumin concentration g / L}\right]).$$

* plasma albumin concentration (mid-normal range)

In a case in which a plasma total calcium concentration was 2.0 mmol/L, for example, the value would be hypocalcemic if the plasma albumin concentration was in the mid-normal range, around 40 g/L. However, in the presence of a low plasma albumin concentration (30 g/L), the corrected plasma total calcium concentration would be 2.25 mmol/L, i.e. normal.

51.4.3 Causes of Hypocalcaemia

The most common cause of acute hypocalcaemia is post-operative hypoparathyroidism, typically in the context of major thyroid surgery. Untreated, the plasma total and ionised calcium concentrations both drop, typically into the plasma total calcium range 1.8–2.0 mmol/L (ionised 0.9–1.0 mmol/L) and the patients exhibit acute symptoms and clinical features of hypocalcaemia. Other causes of hypocalcaemia are provided in Table 51.3.

51.5 Hypercalcemia

As noted above, the normal range for the plasma total calcium concentration is 2.2–2.6 mmol/L (8.8–10.2 mg/dL). Therefore, hypercalcemia is defined by a total calcium concentration >2.6 mmol/L and an ionised Ca^{2+} concentration >1.3 mmol/L. The clinical features of mild hypercalcemia include lethargy, anorexia and constipation. More severe features include muscle weakness, abdominal pain that may be associated

Table 51.3 Causes of hypocalcaemia

Nutritional or metabolic
• Severe vitamin D deficiency
• Chronic kidney disease
Parathyroid dysfunction
• Hypoparathyroidism (surgical or primary)
• Autosomal dominant hypocalcaemia
• PTH resistance states (pseudohypoparathyroidism)
Miscellaneous
• Hungry bone syndrome (e.g. in response to anti-resorptives)
• Acute pancreatitis

Table 51.4 Causes of primary hyperparathyroidism

Benign adenoma: 80%
Benign hyperplasia (all four glands): 20%
Parathyroid carcinoma: <1%
Ectopic PTH (e.g. lung ca): <1%

Table 51.5 Non-PTH-related causes of hypercalcemia

Familial hypocalciuric hypercalcemia
Malignancy
• Multiple myeloma
• Metastatic disease affecting bone (e.g. breast)
• Humoral hypercalcemia of malignancy (PTHrP secreting tumours)
Vitamin D toxicity
Granulomatous disease
• Sarcoidosis
• Tuberculosis
• Inhalation-related granulomas: e.g. talc
Milk Alkali syndrome
Pituitary/adrenal failure

with peptic ulcer disease or pancreatitis, polyuria, and even confusion, convulsions and coma.

In practice, there are two main clinical scenarios according to whether the serum PTH concentration (normal range 1–6 pmol/L) is elevated. If the serum PTH level is elevated, the patient has primary hyperparathyroidism (see Chap. 47) due most commonly to a benign adenoma of a single parathyroid gland (see Table 51.4). If the serum PTH is normal or low, the patient has one of a relatively large number of uncommon causes of hypercalcemia (see Table 51.5). Appropriate investigations for hypercalcemia in the context of (1) raised or (2) normal or low serum PTH levels are provided in Box 51.1 and Box 51.2, respectively. Immobilisation and dehydration can exacerbate hypercalcemia in various contexts including primary hyperparathyroidism.

Box 51.1 Investigations for Hypercalcemia Associated with Elevated Serum PTH Levels

Plasma biochemistry: sodium, potassium, calcium, phosphate, bicarbonate, creatinine, 25-hydroxyvitamin D_3

Urine biochemistry: calcium: creatinine (Ca/Cr ratio)

Serum hormones: PTH

Bone density: DXA

Imaging for parathyroid tumour: Sestamibi scan (neck and thorax); Ultrasound of neck; 4D CT scan (neck and mediastinum)

Box 51.2 Investigations for Hypercalcemia Associated with Normal or Low Serum PTH Levels

Plasma biochemistry: sodium, potassium, calcium, phosphate, bicarbonate, creatinine, 25-hydroxyvitamin D_3. 1,25-dihydroxyvitamin D_3, Angiotensin Converting Enzyme (ACE), ACTH, Cortisol

Urine biochemistry: calcium: creatinine (Ca/Cr ratio)

CXR: granulomas or tumour

Bone density: DXA

51.5.1 Familial Hypocalciuric Hypercalcemia

Familial Hypocalciuric hypercalcemia (FHH) is an uncommon condition that should be considered in patients who present with mild-moderately severe hypercalcemia (total plasma calcium 2.7–3.0 mM) and serum PTH levels that are either normal or at the upper limit of normal. The calcium disturbance is typically benign and does not require medical or surgical intervention. It arises in the context of hyperplasia of all four parathyroid glands. Parathyroid surgery is not indicated. Two key disturbances of calcium metabolism are: (1) impaired inhibitory feedback control of PTH secretion and (2) impaired inhibitory control of renal calcium reabsorption. The elevated serum PTH level arises from impaired calcium-sensing receptor-mediated inhibition of PTH secretion from the parathyroid glands. Hypocalciuria (most easily assessed as the

urinary calcium: creatinine ratio) arises from impaired calcium-sensing receptor (CaSR)-mediated inhibitory control of renal calcium reabsorption. The inappropriately elevated serum PTH concentration and enhanced rate of renal calcium reabsorption act together to raise the plasma calcium concentration. Most commonly, impaired calcium-sensing receptor function in FHH arises from an inactivating mutation of the receptor (Brown et al. 1998).

51.5.2 Forms of FHH That Do Not Arise from Mutations of the CaSR

Recently, two additional genes have been linked to FHH: the alpha subunit of G11 (FHH2) and the sigma subunit of the endosomal sorting protein AP2 (FHH3) (Hannan et al. 2016). FHH has also been described in the context of circulating anti-CaSR antibodies that suppress receptor function.

51.6 Other Disorders of the Calcium-Sensing Receptor

51.6.1 Neonatal Severe Hyperparathyroidism (NSHPT)

Whereas FHH typically arises in individuals who are heterozygous for inactivating mutations of the CaSR, individuals that are, very rarely, homozygous or compound heterozygous for inactivating mutations of the CaSR present early in postnatal life with severe hypercalcemia (plasma total calcium >3.5 mmol/L) and markedly elevated serum PTH concentrations arising from near total failure of Ca^{2+}-dependent feedback control of PTH secretion. This disorder, neonatal severe hyperparathyroidism (NSHPT), requires early four gland parathyroidectomy to correct the disturbance in calcium metabolism, reverse skeletal demineralisation and prevent pathological fractures in the first weeks of life.

51.6.2 Autosomal Dominant Hypocalcaemia

Autosomal dominant hypocalcaemia (ADH) arises from heterozygous activating mutations of the CaSR, which promote renal Ca^{2+} excretion and inappropriately suppress PTH secretion in the context of hypocalcaemia (Brown et al. 1998). Plasma total calcium concentrations typically fall into the range 1.0–1.8 mmol/L (plasma ionised Ca^{2+} 0.5–0.9 mmol/L). Untreated, this condition is usually benign and patients typically report only mild symptoms of hypocalcaemia. Some will report a history of one or more episodes of childhood convulsions. In asymptomatic adults, correction of the plasma calcium concentration into the normal range is not required and is potentially very harmful. Aggressive treatment with oral calcium supplements and active forms of vitamin D such as calcitriol (1,25-dihydroxyvitamin D_3) to restore the plasma calcium to normal, results in marked elevations in renal calcium and phosphate excretion, nephrocalcinosis and associated chronic kidney disease. Some patients treated in this way progress to dialysis and even renal transplantation. For this reason, it is generally accepted that the plasma calcium concentration in patients with ADH should be adjusted, if possible with calcium salts alone, to lie just below the normal range, e.g. between 1.8 and 2.0 mmol/L.

51.6.3 A Form of ADH That Does Not Arise from Mutations of the CaSR

Recently, activating mutations of the alpha subunit of the G-protein G_{11} have been linked to a form of ADH (ADH2) (Hannan et al., 2016).

51.7 Hypercalcemia of Malignancy

51.7.1 Hypercalcemia in the Context of Bone Metastases

Hypercalcemia occurs in the context of osteolytic metastases from various cancers including notably breast cancer and certain forms of leukemia. It arises primarily from markedly enhanced osteoclastic bone resorption in response to cytokines released by the tumour cells in the bone microenvironment. In this context hypercalcemia responds to anti-resorptive therapy, e.g. with the bisphosphonates pamidronate or zoledronate. A similar situation arises in patients with multiple myeloma, a malignancy of plasma cells that arises in the bone marrow and drives enhanced osteoclastic bone resorption.

51.7.2 Humoral Hypercalcemia of Malignancy

In addition to the impact of cancer cells via locally derived cytokines to drive osteoclastic bone resorption in the bone microenvironment, enhanced bone resorption also arises in response to certain cancers that do not metastasise to bone. In these cases (e.g. associated with certain squamous cell carcinomas, renal carcinoma, carcinoma of the ovary, and some lymphomas) markedly enhanced production of cytokines by tumour cells converts peptides that have restricted local roles in certain tissues under normal physiological conditions to factors with endocrine effects. One of these, parathyroid hormone related protein (PTHrP) induces osteoblast-dependent osteoclastic bone resorption via type-1 PTH receptors on osteoblasts (McCauley and Martin 2012). In part, the mechanism involves enhanced osteoblast expression of RANK-ligand and decreased expression of its decoy receptor osteoprotegerin. Under these conditions, RANK-ligand induces osteoclastogenesis, a process in which the number of mature bone-resorbing osteoclasts markedly increases together with the bone-resorbing surface.

51.8 Calcium Disorders in Renal Disease

As chronic kidney disease (CKD) develops there is progressive loss of glomerular filtration, disturbances of renal tubular function and impaired synthesis of key hormones including 1,25 dihydroxyvitamin D_3 and erythropoietin. Elevated plasma phosphate concentration is one early mineral disturbance that arises in the context of the CKD and the plasma phosphate level continues to rise as renal function deteriorates. This is partially offset by increases in the serum FGF-23 and PTH concentrations, at least initially, since FGF-23 and PTH both promote renal phosphate excretion (Uribarri 2007). The plasma calcium concentration is normal initially but falls as the disorder progresses. This promotes the development of secondary hyperparathyroidism, which takes the form of markedly elevated serum PTH levels, including intact PTH as well as various inactive C-terminal fragments, and hyperplasia of all four parathyroid glands. The low plasma calcium concentration, low serum 1,25-dihydroxyvitamin D_3 concentration, high serum PTH levels, and retention of toxic N-containing metabolites, act together to promote the development of renal osteodystrophy, a form of skeletal disease with features of osteoporosis and osteomalacia. Cinacalcet, a positive modulator of the calcium-sensing receptor is used to lower serum PTH levels in CKD to reduce the severity of renal osteodystrophy and reduce bone resorption. To avoid the development of inappropriately low bone turnover rates and thus reduced bone formation rates and repair (‘frozen bone’), the doses of cinacalcet are selected to lower serum PTH concentrations to around 100 pmol/L but not lower. In some CKD patients, hypercalcemia develops late in the disorder (tertiary hyperparathyroidism). In some cases, this arises due to uncontrolled hyperplasia of all four parathyroid glands. In others, single parathyroid adenomas develop.

51.9 Milk Alkali Syndrome

This condition arises typically in the context of high oral dosing with calcium carbonate salts (calcium intakes >4 g/day) (Medarov, 2009). The prevalence of the condition has fallen due to the replacement of calcium carbonate antacids with histamine H_2 receptor antagonists, proton pump inhibitors, and anti-*Helicobacter pylori* antibiotic therapy in the treatment of peptic ulcer disease.

Key features of the condition are hypercalcemia, which can be severe (plasma total calcium concentration >3.0 mmol/L), high plasma bicarbonate levels (>35 mmol/L), alkalosis (arterial or venous pH >7.5), low plasma chloride levels, and renal impairment (plasma creatinine >120 μmol/L). Plasma inorganic phosphate levels are normal rather than low, thereby enhancing the conditions for ectopic mineralisation, and renal calcium excretion levels are inappropriately normal or low, thereby promoting hypercalcemia. Serum PTH and 1,25-dihydroxyvitamin D_3 levels are typically low. The condition may present either acutely or chronically. While the link to the ingestion of both calcium and alkaline salts is clear, the pathogenesis is not well understood. High pH promotes small intestinal Ca^{2+} absorption via the epithelial Ca^{2+} channel Trpv6 and renal Ca^{2+} reabsorption via the epithelial Ca^{2+} channel Trpv5. In addition, high plasma Ca^{2+} levels are reported to suppress glomerular filtration and to promote proximal tubular reabsorption of water and bicarbonate. Finally, chronically elevated plasma concentrations of calcium and bicarbonate together promote the deposition of calcium salts in various tissues including the arterial system, the brain, various structures in the eye including the cornea and lens, and in the kidneys (nephrocalcinosis). Nephrocalcinosis can progress to end-stage renal failure requiring dialysis or renal transplantation.

51.9.1 Management

The approach is relatively simple:

- Stop the calcium and alkaline salts.
- Promote hydration.
- Use frusemide to induce calciuresis if the plasma calcium level is markedly elevated.

In acute cases, the renal function can completely recover. In chronic cases, renal function may be permanently impaired and progression to end-stage kidney disease may occur.

51.10 Nursing Process

51.10.1 Assess

Evaluate all aspects of patient health status, including aspects relating to health promotion, protection and disease prevention, as well as signs and symptoms of calcium disorders.

Hypocalcaemia

– Take a detailed medical history, including specific questions on recent thyroid surgery, osteoporosis and a family history of known calcium disorders or parathyroid dysfunction.
– Assess patient's nutritional state and dietary intake of calcium or vitamin D, sun exposure or recent use of anti-resorptive therapy.
– Inquire about enhanced neuromuscular excitability including fasciculation and tetanic contractions of muscles.
– Examine clinically relevant signs, such as fasciculation and tetanic contractions of isolated muscle groups, by tapping directly over the facial nerve at the angle of the mandible (Chvostek's sign) or by inflating a blood pressure cuff to a level above the systolic pressure for 2–3 min to induce local hypoxemia (Trousseau's sign).

Hypercalcemia

– Assess first on symptoms, especially confusion and lethargy as they are signs of sudden-onset and severe hypercalcemia effecting the nervous system (acute care is needed!)
– Take a detailed medical history including specific questions on kidney stones, chronic kidney disease or renal insufficiency, malignancies and a family history of known calcium disorders.

- Assess patient's nutritional state and dietary intake of calcium or vitamin D and use of supplements or use of calcium and alkaline salts.
- Assess on the mnemonic 'stones, bones, abdominal moans, and psychic groans' (kidney stones, osteoporosis or fractures, pain in abdomen, obstipation and/or depression (and use of lithium)).
- Inquire about urine output, fluid intake and increased thirst.
- Examine clinically relevant signs such as hypotonic muscles, weight loss, dehydration, faecal impaction (from constipation), arrhythmias and or hyper/hypotension.

51.10.2 Diagnose

Work collaboratively to plan appropriate screening tests based on recommendations in patients presenting with calcium disorders.

- Identify patient knowledge on deficits as areas for therapeutic education.
- Ensure appropriate, accurate collection of urine or blood samples for diagnostic or evaluation purpose.
- Ensure appropriate guidance if there is a suspicion of a malignant disease.
- Collaborate with endocrine colleagues to determine if treatment is conform evidence-based guidelines.
- Facilitate additional specialist referrals as needed.

51.10.3 Plan

Interpret test results, recognise abnormal findings and help communicate results and implications to the patient and family.

- Provide disease-specific education to the patient on the long-term effects of the diagnosis and management.
- Advise patient of risks and benefits associated with the various treatment options, including medical and surgical management, and engage the patient in shared decision-making.
- Monitor calcium levels, encourage taking oral fluids, weight-bearing exercises and smoking cessation.
- Instruct what symptoms to report.
- Discuss the expectations of the therapeutic interventions on patient related outcome (what are the patients goals of the treatment) and explain the medical goals.
- Identify patient resources including websites, refer to patient support groups if appropriate.

51.10.4 Implement

Initiate treatment and inform the patient of appropriate monitoring and follow-up.

- Provide therapeutic education (holistic approach) to ensure comprehension of the effects of the diagnosis and management.
- Provide education, support and practical arrangements regarding pre- and post-operative care, make additional referrals as needed (e.g. pre-operative assessment).
- Provide emotional support to patient and family based on condition-specific psychological issues.
- Teach proper administration of medication.
- Plan and coordinate initial and subsequent follow-up appointments.

51.10.5 Evaluate

Assess the effectiveness of interventions and revise the plan of care as appropriate.

- Evaluate biochemical response to treatment.
- Inquire about potential unwanted side effects of the treatment.
- Monitor adherence and compliance to the treatment.
- Assess actual and potential effects on patient-reported outcomes (patients goals, medical goals).
- Monitor for other psychological comorbidities (e.g. anxiety, depression) and coping behaviours.

– Monitor condition-specific issues such as constipation, abdominal pain and fractures.
– Evaluate dietary fluid and calcium intake.
– Evaluate achievement of goals regarding weight-bearing exercises and cessation of smoking.

Case Study Hypercalcemia

A 53-year-old postmenopausal woman who experienced a distal radius fracture was referred to the Fracture Liaison Service (FLS) for investigation of increased fracture risk due to osteoporosis. As part of the screening a DXA scan was performed. She had a consultation with a FLS nurse who took a detailed medical history, explained the results of the DXA scan, assessed the risk for fractures and inquired about other health problems.

Medical history: Kidney stones. Mild depression. Mild hypertension.

Patient-reported health problems: obstipation, dry mouth, anxiety attacks and fear of falling.

Risk factors for fracture (non-modifiable) are:

– Recent fracture
– Age > 50 years
– Mother with hip fracture

Modifiable risk factors:

– Sedentary lifestyle
– Smoking

The results of the DXA scan:

Lumbar spine L1–L4	*T* score −3.2
Femoral neck	*T* score −2.6
Vertebral fracture assessment (Th4-L5)	No significant vertebral fractures

Diagnosis conform WHO criteria: Severe osteoporosis

The nurse explains the implications of having an increased fracture risk and the need for further investigation. She orders a chemistry panel to screen for underlying causes of osteoporosis, including: electrolytes, 25OH vitamin D, Serum calcium, Albumin, Creatinine, PTH, TSH, Alkaline phosphatase and Serum phosphate. And refers the patient to the endocrinologist (who is participating in the FLS programme).

Lab results:

Electrolytes, albumin, creatinine, TSH: within normal range
25OH vitamin D: 97 nmol/L,
Serum calcium: 2.93 mmol/L
PTH: 17 pmol/L
Alkaline phosphatase: 130 IU/L
Serum phosphate: 2.6 mg/dL

Additional investigation of calcium excretion in 24H urine sample shows increased levels of calcium. Physical investigation shows no abnormalities besides a mild hypertension. There are no signs of malignant diseases.

These results suggest primary hyperparathyroidism.

The next step in the diagnostic process is to perform a sestamibi scan and an ultrasound. These diagnostic imaging tests show hyperplasia of one of the parathyroid glands diagnosed as a solitary parathyroid adenoma.

Because there is a symptomatic primary hyperthyroidism and (secondary) osteoporosis, the patient is referred to the head-neck surgeon who performs an extirpation of the parathyroid gland. The PTH levels normalise completely after surgery. The osteoporosis is treated with a weekly dosed oral bisphosphonate.

The patient experienced difficulties coping with these three diagnoses (fracture, osteoporosis and hyperparathyroidism) and their treatment (surgery, medication). Although she was thankful for finding the probable cause of multiple health problems, it was a lot to deal with. The patient is guided by a Nurse Practitioner (NP) who provides practical and emotional support. Three months after surgery the patient reports an increased quality of life and is completely symptom free. The patients next challenges are cessation of smoking and staying compliant to the bisphosphonates.

51.11 Conclusions

Calcium and phosphate are subject to homeostatic control mechanisms due to their importance as key chemical components of the bone mineral hydroxyapatite and key roles as important ionic species in physiologically important cell functions. In plasma calcium is present in three main forms, its ionised form Ca^{2+} (normally around 50% of the total), an albumin-bound form that is pH-sensitive (around 45% of the total), and as complexes with small organic molecules such as citrate (around 5% of the total). For this reason, the ionised Ca^{2+} concentration (normal range 1.1–1.3 mM) is only around half of the total plasma calcium concentration (normal range 2.2–2.6 mM). Inorganic phosphate is present in plasma in two main forms, the dibasic form HPO_4^{2-} and the monobasic form $H_2PO_4^-$ in a ratio of around 5:1 at physiological pH, 7.4. The calcium concentration in plasma is tightly regulated dependent on the operation of calcium-sensing receptors (CaSRs) in the parathyroid gland and in several tubular segments in the kidneys. The key role of CaSRs in both parathyroid and kidney is to lower the plasma calcium concentration. The key role of PTH is to prevent and/or correct hypocalcaemia. Once activated, the key role of vitamin D is to promote calcium and phosphate absorption from the intestine and to promote calcium reabsorption from the kidneys. The daily requirements of calcium approximate 1.0 g for adults but this increases in certain circumstances, e.g. pregnancy and lactation.

There are a large number of causes of hypocalcaemia and hypercalcemia. Careful investigation is required to identify the cause and select an appropriate plan of management. In general, acute disturbances of the plasma calcium concentration require early intervention. Acute *hypocalcaemia* arises chiefly in the context of thyroid or parathyroid surgery due to the inadvertent removal/damage of normal parathyroid tissue, or in the context of anti-resorptive therapy in patients with osteoporosis, who are vitamin D deficient (serum 25-hydroxyvitamin D <40 nmol/L). Acute pancreatitis is another important cause. Acute *hypercalcemia* arises in the context of malignancy (bone metastases or HHM), vitamin D toxicity and milk alkali syndrome. Factors that can exacerbate hypercalcemia include immobilisation, dehydration and treatment with thiazide diuretics.

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