3

Alkaline Earth Metals

Members of group 2 of the periodic table (second vertical column) are called *earth alkaline metals*. In this group are included the following elements: beryllium (Be), magnesium (Mg), calcium (Ca), strontium (Sr), barium (Ba) and radium (Ra). Radium is a radioactive element and therefore we will not further discuss it in this chapter (Figure 3.1).

In terms of clinical use, magnesium and calcium are essential ions for the human body and any of their imbalances should be corrected. Strontium is medically used in radiotherapy, and its application is further discussed in Chapter 10. Exposure to excess beryllium can lead to the so-called chronic beryllium disease (CBD), which is discussed later in this chapter. Barium salts are generally highly toxic. Nevertheless, the so-called barium meal is a well-used oral radio-contrast agent.

3.1 Earth alkaline metal ions

Earth alkaline metals together with the alkali metals form the so-called s-block metals. Earth alkaline metals have two electrons in their outer shell which is an s-orbital type. The chemistry of the metals is characterised by the loss of both electrons, which is a result of the relatively low ionisation energy (IE) of both electrons and the subsequent formation of the stable cation M^{2+}, which has a noble gas configuration (Table 3.1).

Group 2 elements are all silvery-white metals with high reactivity, similar to alkali metals, but less soft and not as reactive. Earth alkaline metals can be mostly found in the earth's crust in the form of their cations displayed in minerals and not as the elemental metal, as these are very reactive. For example, beryllium principally occurs as beryl ($Be_3Al_2[Si_6O_{18}]$), which is also known as *aquamarine*.

Magnesium can be found in rock structures such as magnesite ($MgCO_3$) and dolomite ($MgCO_3{\cdot}CaCO_3$), and is the eighth most abundant element in the earth's crust. Calcium is the fifth most abundant element and can be found in minerals such as limestone ($CaCO_3$) and its metamorphs such as chalk and marble.

Earth alkaline metals are harder and have a higher density than sodium and potassium and higher melting points. This is mostly due to the presence of two valence electrons and the resulting stronger metallic bond. Atomic and ionic radii increase within the group, and the ionic radii are significantly smaller than the atomic radii. Again, this is due to the existence of two valence electrons, which are located in the s orbital furthest from the nucleus. The remaining electrons are attracted even closer to the nucleus as a result of the increased

Essentials of Inorganic Chemistry: For Students of Pharmacy, Pharmaceutical Sciences and Medicinal Chemistry,
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H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub						

Figure 3.1 *Periodic table of elements; group 2 elements are highlighted*

Table 3.1 *First, second and third ionisation energies (kJ/mol) of group 2 metals [1]*

	First	Second	Third
Be	900	1 757	14 847
Mg	738	1 450	7 731
Ca	590	1 145	4 910
Sr	550	1 064	4 207
Ba	503	965	3 600

Source: Reproduced with permission from [8]. Copyright © 1996, John Wiley & Sons, Ltd.

effective nuclear charge. The IEs of the first two valence electrons are similar and relatively low compared to the energy needed to remove the third valence electron, which is part of a fully filled quantum shell. As a result, the dominant oxidation state of earth alkaline metals is +2.

3.1.1 Major uses and extraction

Beryllium is one of the lightest metals and therefore is used in high-speed aircrafts and missiles. Unfortunately, it is highly toxic, and CBD, a scarring of the lung tissue, is often seen in workers from within a beryllium-contaminated work environment.

Calcium is mostly found in limestone and its related forms, such as chalk, and marble and lime (CaO). Ca^{2+} ions are essential for living organisms, as is Mg^{2+}. Magnesium is the only earth alkaline metal that is used on an industrial scale. It is used in ammunition (e.g. tracer bullets and incendiary bombs), as it burns with a very bright white glow. Magnesium alloyed with aluminium results in a low-density and strong material, which is used for lightweight vehicles and aeroplanes.

Magnesium is the only group 2 element that is extracted on a large scale. Its main source is seawater, and the metal is extracted by adding calcium hydroxide. Magnesium hydroxide precipitates, as it is less soluble in water compared to the calcium compound. Magnesium hydroxide is converted into magnesium chloride

Conversion $2HCl + Mg(OH)_2 \rightarrow MgCl_2 + 2H_2O$

Electrolysis: at the cathode: $Mg^{2+}_{(l)} + 2e^- \rightarrow Mg_{(l)}$

at the anode: $2Cl^-_{(l)} \rightarrow Cl_{2(g)} + 2e^-$

Redox: $2Mg^{2+} + 2Cl^- \rightarrow 2\,Mg_{(l)} + Cl_{2(g)}$

Figure 3.2 *Redox equation for the production of magnesium*

Calcination : Dolomite $[CaMg(CO_3)_2]$ is converted into MgO and CaO

Reduction : $2MgO + 2CaO + FeSi \rightarrow 2Mg + Ca_2SiO_4 + Fe + 1450\,K$

Figure 3.3 *Chemical equation for the production of magnesium*

($MgCl_2$), which can be subsequently electrolysed in a Down's cell (see Section 2.1.1) in order to produce the pure magnesium metal (Figure 3.2).

Alternatively, there is a second method called the *ferrosilicon process* or *pigeon process*. This involves the reduction of magnesium oxide, which is obtained from dolomite, with an iron–silicon alloy. The raw material has to be calcined first, which means the removal of water and carbon dioxide, as these would form gaseous by-products and would reverse the subsequent reduction (Figure 3.3).

3.1.2 Chemical properties

The chemical behaviour of alkaline earth metals is characterised by their strong reducing power, and therefore they very easily form bivalent cations (M^{2+}). The elements within group 2 become increasingly more electropositive on descending within the group.

The **metals** themselves are coloured from grey (Be, Mg) to silver (Ca, Sr, Ba) and are soft. Beryllium and magnesium are passivated and therefore kinetically inert to oxygen or water. The metal barium has to be stored under oil because of its reactivity. Metals such as calcium, strontium and barium react similar to sodium, but are slightly less reactive: All the metals except beryllium form oxides in air at room temperature once the reaction is started. The nitride compound is formed in the presence of nitrogen, and magnesium can burn in carbon dioxide, which means that magnesium fires cannot be extinguished by the use of carbon dioxide fire extinguishers.

$$2M + O_2 \rightarrow 2MO \qquad 3M + N_2 \rightarrow M_3N_2$$

$$2Mg_{(s)} + CO_{2(g)} \rightarrow 2MgO_{(s)} + C_{(s)}$$

The **oxides** of alkaline earth metals have the general formula MO and are generally basic. Beryllium oxide (BeO) is formed by the ignition of beryllium metal in an oxygen atmosphere. The resulting solid is colourless and insoluble in water. Other group 2 oxides (MO) are typically formed by the thermal decomposition of the corresponding metal carbonate or hydroxide.

$$MCO_3 \rightarrow MO + CO_2$$

$$Be(OH)_2 + 2(OH)^- \rightarrow [Be(OH)_4]^{2-}$$

$$Be(OH)_2 + H_2SO_4 \rightarrow BeSO_4 + 2H_2O$$

Figure 3.4 *Chemical equations showing the amphoteric nature of beryllium hydroxide*

Peroxides are known for magnesium, calcium, strontium and barium but not for beryllium. The radius of the beryllium cation (Be^{2+}) is not sufficient to accommodate the peroxide anion.

Beryllium reacts with aqueous alkali (NaOH) and forms beryllium **hydroxide**, which is an amphoteric hydroxide.

*The term **amphoteric** describes compounds that can act as an acid and a base.*

Beryllium hydroxide reacts with a base with the formation of the corresponding beryllium salt. Beryllium hydroxide can also be reacted with acids such as sulfuric acid and the corresponding salt, beryllium sulfate, is obtained (Figure 3.4).

Magnesium does not react with aqueous alkali (NaOH). The synthesis of magnesium hydroxide [$Mg(OH)_2$] is based on a metathesis reaction in which magnesium salts are reacted with sodium or potassium hydroxide.

$$Mg^{2+}_{(aq)} + 2KOH_{(aq)} \rightarrow Mg(OH)_{2(s)} + 2K^+ \tag{3.1}$$

Calcium, strontium and barium oxides react exothermically with water to form the corresponding hydroxides:

$$CaO_{(s)} + H_2O_{(l)} \rightarrow Ca(OH)_{2(s)}$$

$$SrO_{(s)} + H_2O_{(l)} \rightarrow Sr(OH)_{2(s)}$$

$$BaO_{(s)} + H_2O_{(l)} \rightarrow Ba(OH)_{2(s)} \tag{3.2}$$

Magnesium and calcium hydroxides are sparingly soluble in water and the resulting aqueous solutions are mildly alkaline. In general, group 2 hydroxides, except $Be(OH)_2$, react as bases, and their water solubility and thermal stability increase within the group (Mg→Ba).

Earth alkaline halides (MCl_2) are normally found in their hydrated form. Anhydrous beryllium **halides** are covalent, whereas Mg(II), Ca(II), Sr(II), Ba(II) halides are ionic. As a result of the ionic bond, the later halides have typically high melting points and they are sparingly soluble in water. Additionally, $MgCl_2$, $MgBr_2$, MgI_2 are hygroscopic. Anhydrous calcium chloride also has a strong affinity for water and is typically used as a drying agent.

***Hygroscopic compounds** are substances that absorb water from the surrounding air but do not become a liquid.*

3.2 Beryllium and chronic beryllium disease

The element beryllium can be found in the mineral beryl [$Be_3Al_2(SiO_3)_6$] and has minor but important technical applications. Owing to its unique properties, it is used in industrial lightweight systems, for example,

turbine rotor blades, automotive parts and electrical contacts. The pure beryllium metal is also used in the nuclear industry.

Beryllium has an exceptionally small atomic radius, and as a result beryllium fluoride, chloride and oxide show evidence of covalent bonds in contrast to the other group 2 oxides or halides. Beryllium halides should be linear if they exhibit the ionic bonding character. This linear form can only be found in the gas phase. In the solid state, the beryllium centre is three or fourfold coordinated, which can be achieved, for example, by polymerisation.

Beryllium and its compounds are extremely poisonous and therefore there is only a very limited potential for their clinical applications. Indeed, even the inhalation of beryllium or its compounds can lead to serious respiratory diseases such as the *chronic beryllium disease*, and soluble beryllium compounds can cause serious skin irritations. Workers within the metal production industry are most likely exposed to beryllium and run the highest risk of developing CBD. But also people working in connected professions such as administrative staff or families are at high risk of beryllium poisoning. Symptoms are not well reported, may occur many years after the exposure and include cough, fatigue and chest pain, whereas nonrespiratory organs can also be affected. However, the introduction of exposure limits and general awareness of the risk have significantly reduced the risk of beryllium exposure and its consequences [2].

3.3 Magnesium: competition to lithium?

The element magnesium (Mg) is a silvery-white and lightweight metal. It is protected by a thin oxide layer, which is very difficult to remove but at the same time removes the need to store it in an oxygen-free environment (see alkali metals). Magnesium reacts with water but much more slowly than its neighbouring earth alkaline metal calcium. Magnesium is a highly flammable metal, and once ignited it burns with a characteristic bright white flame. There are three stable isotopes of magnesium, namely ^{24}Mg (79% occurrence), ^{25}Mg and ^{26}Mg. ^{28}Mg is radioactive with a half-life of 21 h [1].

Most magnesium salts are soluble in water, and given in large amounts they work as a laxative in the human body. Aqueous magnesium ions are sour in taste. Magnesium hydroxide ($MgOH_2$) has only limited solubility in water and the resulting suspension is called *milk of magnesia*, which is commonly used as an antacid and is known to be a mild base. Magnesium is extracted on a large scale using a Down's cell (see Section 2.1.1) or the ferrosilicon process with seawater being the main source (see Section 3.1.1). Mg^{2+} stands in a so-called diagonal relationship to Li^+, which explains why these ions have similar properties and biological activity (see Section 2.2.4).

3.3.1 Biological importance

Mg^{2+} is an essential ion in the human body and is a crucial constituent in numerous enzymatic processes. Indeed, Mg^{2+} is essential to most living cells as a signalling molecule and is involved in nucleic acid biochemistry dealing with the manipulation of ATP (adenosine triphosphate), DNA, RNA and related processes. For example, ATP has to be coordinated to a magnesium ion in order to become biologically active. Mg^{2+} also stabilises DNA and RNA structures, which can be seen in their increased melting points.

Mg^{2+} ions form the redox-active centre in chlorophyll, which facilitates the process of photosynthesis and the connected carbon fixation in green plants. Therefore, green vegetables, as well as milk, whole grain and nuts, are good sources of magnesium. It has to be kept in mind that most magnesium salts are water soluble and therefore processed vegetables, mainly cooked in water, are low in magnesium ion content.

In the human body, Mg^{2+} is the fourth most abundant cation and the second most abundant ion in the interstitial fluid. Mg^{2+} is an essential co-factor dealing with more than 300 cellular enzymatic processes.

On average, the human body contains about 24 g of magnesium ions, with half of it being incorporated into bones and the other half being present in muscles and soft tissue. The majority of Mg^{2+} is absorbed in the ilium and colon, and the kidneys are the major excretory organ. Mg^{2+} is filtered at the glomerulus, and 10–15% is re-absorbed at the proximal tubule, 60–70% at the thick part of the ascending limb of the loop of Henle and 10–15% at the distal tubule [3].

Nevertheless, magnesium salts are generally not well absorbed from the gastrointestinal (GI) tract and therefore are often used as osmotic laxatives. The kidneys regulate the magnesium ion levels in plasma, and as a result high levels of Mg^{2+} are retained when the patient has renal failure. The resulting hypermagnesia can cause muscle weakness and arrhythmia, but it is a rare condition. Hypomagnesia, defined as low magnesium levels in the blood plasma, can be the result of losses in the GI tract, for example, excessive diarrhoea. Magnesium imbalances can also be a result of alcoholism or secondary to treatment with certain drugs. Hypomagnesia is often followed by hypocalcaemia (low calcium ion plasma levels) as well as hypokalaemia and hyponatraemia [3, 4].

3.3.2 Clinical applications and preparations

Magnesium ion imbalances can manifest in a variety of conditions such as hypo- and hypermagnesaemia. Magnesium ion preparations are also used as antacids, mostly in combination with aluminium-based salts (see Section 4.3.5). Additionally, magnesium salts are involved in the treatment of arrhythmia (irregular heart beat) and eclampsia, a life-threatening hypertensive disorder in pregnant women.

Symptomatic hypomagnesaemia is associated with plasma serum Mg^{2+} levels of <0.5–1 mmol/kg for a period of 5 days or more. Mg^{2+} ions are initially given as intravenous (i.v.) or intramuscular injection; the latter is fairly painful and consisting of magnesium sulfate ($MgSO_4$). $MgSO_4$ can also be used as emergency treatment for very serious arrhythmias, a disorder of the heart rate (pulse). In an emergency treatment, it is usually given intravenously as one single dose or with one repeat (Figure 3.5) [4, 5].

Note that the plasma magnesium concentration should be monitored, and the dose has to be reduced in patients with renal impairment as Mg^{2+} is excreted via the kidneys. Magnesium ions can also be given orally to the patient, for example, in the form of magnesium glycerophosphate tablets.

Magnesium hydroxide [$Mg(OH)_2$] is present in antacids because of its laxative properties and is also the main ingredient of the 'milk of magnesia'. The 'milk of magnesia' is a suspension of $Mg(OH)_2$ in water, which has a milk-like appearance because of the low aqueous solubility of $Mg(OH)_2$. It is considered as a strong electrolyte and a weak base and is given to the patient for indigestion and heartburn. The alkaline suspension neutralises any excess stomach acid and therefore works as an antacid. It also stimulates intestinal movement, as the magnesium ions increases the water content in the intestines through its osmotic effect and as a result softens any faeces present.

Magnesium trisilicate ($Mg_2Si_3O_8$) can also be used in antacid preparations especially in the treatment of peptic ulcers. The mode of action includes the increase of the pH of the gastric fluid together with the formation of a colloidal silica precipitate, which forms a protection for the GI mucosa. Most antacids contain a mixture of

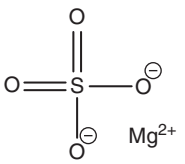

Figure 3.5 *Structure of $MgSO_4$*

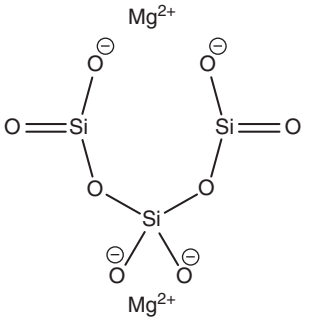

Figure 3.6 *Chemical structure of magnesium trisilicate ($Mg_2Si_3O_8$)*

aluminium hydroxide [$Al(OH)_3$] and magnesium and/or calcium preparations. Therefore, the mode of action will be further discussed in the chapter on aluminium-based drugs (see Section 4.3.5) (Figure 3.6).

Unfortunately, orally taken magnesium salts can show interactions with other drugs taken simultaneously. Magnesium trisilicate reduces the absorption of iron products, certain antibiotics (such as Nitrofurantoin) or antimalarial drugs (such as Proguanil). Magnesium salt preparations, which form part of antacids, are not recommended to be taken at the same time as a variety of drugs such as ACE inhibitors, aspirin and penicillamine. In most cases, antacids reduce the absorption of the simultaneously taken drug. Therefore, before any treatment with antacids, the full medical history of the patient should be taken and possible interactions assessed [4].

3.4 Calcium: the key to many human functions

Calcium is the most abundant inorganic element in the human body and is an essential key for many physiological processes. Ca^{2+} has numerous intra and extracellular physiological roles, for example, a universal role as messenger and mediator for cardiac, skeletal and smooth muscle contractions. Calcium ions are a critical factor in several life-defining biochemical processes as well as in the endocrine, neural and renal aspects of blood pressure homeostasis.

Calcium has the symbol Ca and atomic number 20 and is a soft grey alkaline earth metal. Calcium has four stable isotopes (^{40}Ca and ^{42}Ca–^{44}Ca) and the metal reacts with water with the formation of calcium hydroxide and hydrogen.

$$2Ca + 2H_2O \rightarrow 2CaOH + H_2 \tag{3.3}$$

Calcium salts can be found in everyday life. Limestone, cement, lime scale and fossils are only a few examples where we encounter Ca^{2+}. They also have a wide spectrum of applications spanning from insecticides to clinical applications. Calcium arsenate [$Ca_3(AsO_4)_2$] is extremely poisonous and is used in insecticides. Calcium carbonate ($CaCO_3$) can be found in clinical applications such as antacids, but note that an excessive intake can be hazardous. Calcium chloride ($CaCl_2$) is used in ice removal and dust control on dirt roads, as a conditioner for concrete and as an additive in canned tomatoes. Calcium cyclamate [$Ca(C_6H_{11}NHSO_4)_2$] is used as a sweetening agent, and calcium gluconate [$Ca(C_6H_{11}O_7)_2$] is used as a food additive in vitamin pills. Calcium hypochlorite $Ca(OCl)_2$ can be found in swimming pool disinfectants, in bleaching agents, in deodorants and in fungicides. Calcium permanganate [$Ca(MnO_4)_2$] is used in textile production, as a water-sterilising agent and in dental procedures. Calcium phosphate [$Ca_3(PO_4)_2$] finds

applications as a supplement for animal feed, as a fertiliser, in the manufacture of glass and in dental products. Calcium sulfate ($CaSO_4 \cdot 2H_2O$) is the common blackboard chalk.

3.4.1 Biological importance

Calcium ions play important roles in the human body in a variety of neurological and endocrinological processes. Calcium is known as a *cellular messenger* and it has a large intra- versus extracellular gradient (1 : 10 000), which is highly regulated by hormones. This gradient is necessary to maintain the cellular responsiveness to diverse extracellular stimuli. Calcium ions are also involved in the formation of bones and teeth, which act also as a reservoir for calcium ions.

A normal adult body contains ~1000 g of calcium, of which around 99% are extracellular and most of which is stored in bones and teeth. Bones actually serve as a dynamic store for Ca^{2+}. The remaining 1% of Ca^{2+} can be found in the extracellular space, such as plasma, lymph and extracellular water. The intra and extracellular Ca^{2+} concentration is extremely important to many physiological functions and is therefore rigorously controlled (Figure 3.7) [6].

Calcium ions are regulated within the gut, skeleton and kidneys. The Ca^{2+} homeostasis is normally in equilibrium, which means that the amount of Ca^{2+} enters the body is equal to the amount of Ca^{2+} leaving the body. Calcium ion levels are regulated by hormones that are not regulated by the Ca^{2+} level, called *noncalciotropic hormones*, for example, sex hormones and growth factors. In contrast, there are hormones that are directly related to Ca^{2+}, for example, PTH (parathyroid hormone), which are called *calciotropic hormones*. PTH controls the serum plasma level of Ca^{2+} by regulating the re-absorption of Ca^{2+} in the nephron, stimulating the uptake of Ca^{2+} from the gut and releasing Ca^{2+} from the bones which act as a reservoir.

Modified hydroxylapatite, also frequently called *hydroxyapatite* and better known as *bone mineral*, makes up ~50% of our bones. Hydroxylapatite is a natural form of the mineral calcium apatite, whose formula is

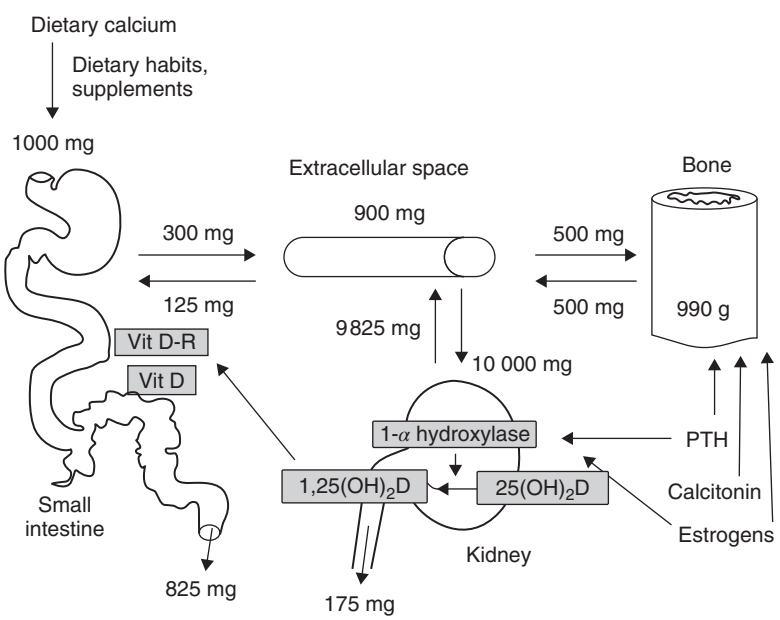

Figure 3.7 *Calcium homeostasis [6] (Reproduced with permission from [6]. Copyright © 2005, John Wiley & Sons, Ltd.)*

usually denoted as $Ca_{10}(PO_4)_6(OH)_2$. Modifications of hydroxylapatite can also be found in the teeth, and a chemically identical substance is often used as filler for replacement of bones, and so on. Nevertheless, despite similar or identical chemical compositions, the response of the body to these compounds can be quite different.

3.4.2 How does dietary calcium intake influence our lives?

It is believed that an optimal dietary calcium intake can prevent chronic diseases. In the Stone Age, the average calcium intake was 2000–3000 mg Ca^{2+}/day per adult, whereas now-a-days it has decreased to an average of 600 mg/day [7]. This means that we are living in permanent calcium deficiency, and it is believed that there are linkages to various chronic diseases, such as bone fragility, high blood pressure and colon cancer [8].

Ca^{2+} is an essential nutrient, and the required amount varies throughout a person's life time depending on the stage of life. There have been three stages of life identified when the human body needs an increased level of Ca^{2+}. The first one is childhood and adolescence because from birth to the age of ~18 the bones form and grow until they reach their maximum strength. Pregnancy and lactation has also been identified as a time when the human body is in need of an increased level of Ca^{2+}. A full infant accumulates around 30 g of Ca^{2+} during gestation and another 160–300 mg/day during lactation. Ageing has been identified as the third period of life in humans when increased calcium intake is required. This has been associated with several changes to the calcium metabolism in the elderly (Table 3.2).

3.4.3 Calcium deficiency: osteoporosis, hypertension and weight management

Osteoporosis is most commonly associated with calcium deficiency, but an adequate calcium intake should not only be considered as a therapy for bone loss. It should be seen as an essential strategy for the maintenance

Table 3.2 *Optimal daily calcium intake according to NIH Consensus Conference [6]*

Age	mg/d
Neonates	
0–6 mo	400
6–12 mo	600
Children	
1–5 yr	800
6–10 yr	800–1200
Adolescents	
11–24 yr	1200–1500
Male adults	
25–65 yr	1000
Elderly	1500
Female adults	
20–25 yr	1000
Pregnant and nursing	1200–1500
Postmenopausal (>50 yr)	1500
Elderly (>65 yr)	1500

Source: Reproduced with permission from [6]. Copyright © 2005, John Wiley & Sons, Ltd.

of health in the ageing human. Ninety-nine percent of Ca^{2+} is found in the bones, as they function as a reservoir. Osteoporosis is known to be the major underlying cause on bone fractures in postmenopausal women. Calcium uptake and plasma concentrations are closely regulated by hormones, as outlined in Section 3.4.1. Nevertheless, there has been no clear and direct relationship between Ca^{2+} intake and bone health established until now. It is believed that a high Ca^{2+} concentration and vitamin D level is essential in the first three decades of life in order to establish an optimum bone density level. These also modify the rate of bone loss, which is associated with ageing.

Studies support the hypothesis that calcium supplementation can reduce blood pressure, being more beneficial to salt-dependent hypertension. The regulation of the cellular calcium metabolism is central to blood pressure homeostasis. It is believed that the higher the level of cytosolic-free calcium ions, the greater the smooth muscle vasoconstrictor tone, which in turn has an effect on the sympathetic nervous system activity and thus on the blood pressure. Nevertheless, studies do not justify the use of calcium supplementation as the sole treatment for patients with mild hypertension.

It has been hypothesised that there exists a link between dietary calcium and weight management in humans. It has been proposed that a low-calorie, high-Ca^{2+} diet helps in supporting the fight against obesity and increase the energy metabolism. The recommended Ca^{2+} intake should be around 1200 mg/day as previously mentioned depending on the age. Available evidence indicates that increasing the calcium intake may substantially reduce the risk of being overweight, although long-term, large-scale prospective clinical trials need to be conducted to confirm or better clarify this association.

3.4.4 Renal osteodystrophy

Renal osteodystrophy, also called *renal bone disease*, is a bone mineralisation deficiency seen in patients with chronic or end-stage renal failure.

Vitamin D is usually activated in the liver to the pro-hormone calcidiol and then in the kidney to calcitriol, which is the active form of vitamin D. Both activation steps are based on a hydroxylation reaction. Pro-vitamin D is hydroxylated in the 25 position in the liver (calcidiol) and then in the kidney at the 1α-position (calcitriol). Calcitriol helps the body to absorb dietary Ca^{2+} (Figure 3.8).

In patients with renal failure, the activation to calcitriol is depressed, which results in a decreased concentration of Ca^{2+} in the blood plasma. Furthermore, the plasma phosphate level increases as a result of the kidney impairment. This, in turn, reduces the amount of free Ca^{2+} in the blood even more, as the phosphate complexes the free Ca^{2+}. The pituitary gland senses the low levels of plasma Ca^{2+} and releases PTH. As previously outlined, PTH increases the re-absorption of Ca^{2+} in the nephron and absorption in the gut, and promotes the release of Ca^{2+} from the bones. In turn, this leads to a weakening of the bone structure.

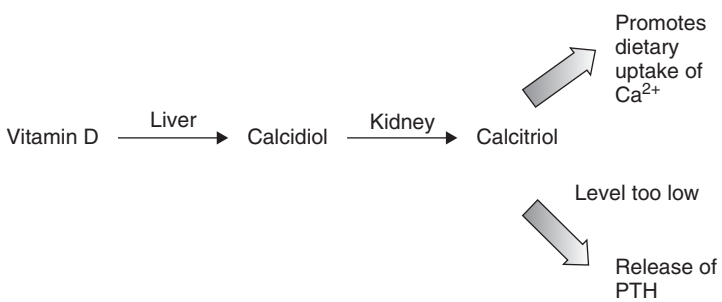

Figure 3.8 *Activation of vitamin D*

Patients can be treated with phosphate binders in order to avoid excess phosphate absorption from the gut. Dialysis will also be helpful in removing excess phosphate from the blood. Furthermore, the patient can be given synthetic calcitriol and potentially calcium supplements.

3.4.5 Kidney stones

Around 20–40% of all kidney stones are associated with elevated Ca^{2+} level in the urine. For a long time, it has been suggested that low dietary calcium intake would be the best method to prevent the recurrence of kidney stones. More recent studies involving patients who suffered from recurring calcium oxalate stones showed that a low calcium diet did not prevent the formation of kidney stones. It was actually found that a higher calcium intake of around 1200 mg/day resulted in a significant reduction of the recurrence of kidney stones by around 50%. It is believed that the restriction of calcium leads to an increase in absorption and excretion of oxalate in the urine and therefore promotes the formation of calcium oxalate stones. Currently, the conclusion is that kidney stone formation in healthy individuals is not associated with calcium supplementation [4].

3.4.6 Clinical application

Calcium supplements are usually required only if the dietary Ca^{2+} intake is insufficient. As previously mentioned, the dietary requirements depend on the age and circumstances; for example, an increased need can be seen in children, in pregnant women and in the elderly where absorption is impaired. In severe acute hypocalcaemia, a slow i.v. injection of a 10% calcium gluconate has been recommended. It has to be kept in mind that the plasma Ca^{2+} level and any changes to the electrocardiogram (ECG) have to be carefully monitored [5].

A variety of calcium salts are used for clinical application, including calcium carbonate, calcium chloride, calcium phosphate, calcium lactate, calcium aspartate and calcium gluconate. Calcium carbonate is the most common and least expensive calcium supplement. It can be difficult to digest and may cause gas in some people because of the reaction of stomach HCl with the carbonate and the subsequent production of CO_2 (Figure 3.9).

Calcium carbonate is recommended to be taken with food, and the absorption rate in the intestine depends on the pH levels. Taking magnesium salts with it can help prevent constipation. Calcium carbonate consists of 40% Ca^{2+}, which means that 1000 mg of the salt contains around 400 mg of Ca^{2+}. Often, labels will only indicate the amount of Ca^{2+} present in each tablet and not the amount of calcium carbonate (Figure 3.10).

$$CaCO_3 + 2HCl \rightarrow CO_2 + CaCl_2 + H_2O$$

Figure 3.9 *Chemical equation showing the synthesis of CO_2 under acidic stomach conditions*

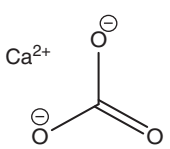

Figure 3.10 *Chemical structure of calcium carbonate*

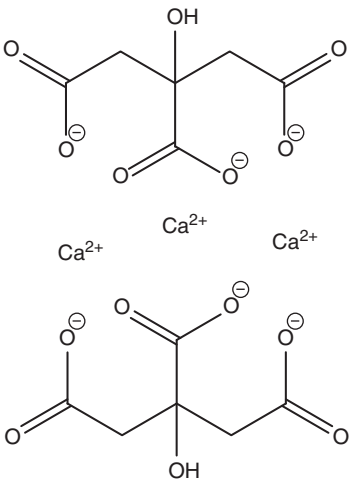

Figure 3.11 *Chemical structure of calcium citrate*

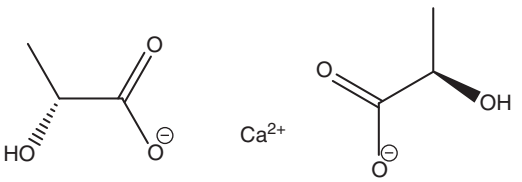

Figure 3.12 *Chemical structure of calcium lactate*

Calcium citrate is more easily absorbed (bioavailability is 2.5 times higher than calcium carbonate); it is easier to digest and less likely to cause constipation and gas than calcium carbonate. Calcium citrate can be taken without food and is more easily absorbed than calcium carbonate on an empty stomach. It is also believed that it contributes less to the formation of kidney stones. Calcium citrate consists of around 24% Ca^{2+}, which means that 1000 mg calcium citrate contains around 240 mg Ca^{2+}. The lower Ca^{2+} content together with the higher price makes it a more expensive treatment option compared to calcium carbonate, but its slightly different application field can justify this (Figure 3.11).

The properties of calcium lactate are similar to those of calcium carbonate [9], but the former is usually more expensive. Calcium lactate contains effectively less Ca^{2+} per gram salt than, for example, calcium carbonate. Calcium lactate consists of only 18% Ca^{2+}, making it a less 'concentrated' salt (Figure 3.12) [10].

Calcium gluconate is prescribed as a calcium supplement, but it is also used in the urgent treatment of hyperkalaemia (K^+ plasma levels above 6.5 mmol/l). Hyperkaleamia in the presence of ECG changes usually requires immediate treatment, and a 10% calcium gluconate solution intravenously administered is recommended (see Section 2.4.4). Administration of the calcium solution does not lower the plasma K^+ level but protects temporarily against myocardial excitability and therefore temporarily reduces the toxic effects of hyperkalaemia. Calcium gluconate contains effectively the least Ca^{2+} per amount of supplement (only around 9%). That means that in 1000 mg calcium gluconate, only 90 mg is actual Ca^{2+} (Figure 3.13).

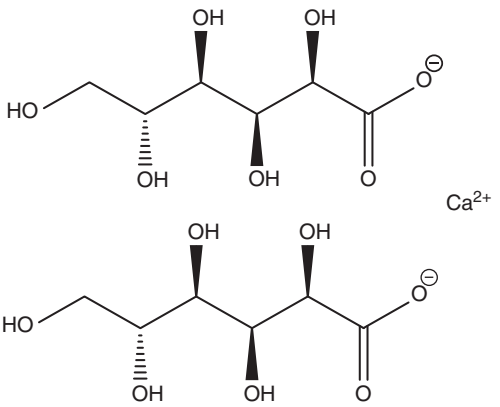

Figure 3.13 *Chemical structure of calcium gluconate*

3.4.7 Side effects

Several large long-term studies have shown that a daily intake of 1000–2500 mg of calcium salts is safe. Side effects have been observed only at relatively high doses, being manifested in GI disturbances such as constipation and bloating and, in extreme cases, arrhythmia [11]. The GI system normally adjusts after a while, and problems should resolve themselves. Calcium salts are generally better absorbed in an acid environment, so patients with a low production of stomach acid or elderly patients who are on high doses of antiulcer medication might experience problems with absorption. It is then recommended to consume the calcium supplement with a meal [5].

Nevertheless, it is important to note that calcium ions can interfere with the absorption of some drugs, such as antibiotics. For example, tetracycline and quinolone antibiotics can chelate Ca^{2+} ions and form complexes which cannot be absorbed anymore. Therefore, calcium supplements and antibiotics should not be taken together. Patients are typically advised to take antibiotics 1 h before or 2 h after food [5].

3.5 Barium: rat poison or radio-contrast agent?

The element barium (Ba) has the atomic number 56 and is classified as a heavy metal. Barium metal is highly reactive and therefore no elemental barium exists in nature. Natural sources of barium are the water-insoluble minerals barite (barium sulfate) and whiterite (barium carbonate). In order to obtain pure barium compounds, the mineral barite is reacted with carbon, and barium sulfide is formed. Barium sulfide is, in contrast to barium sulfate, water soluble. Subsequently, the pure barium sulfide is treated with sulfuric acid and pure barium sulfate can be obtained.

$$BaSO_4 + 4C \rightarrow BaS + 4CO$$

$$BaS + H_2SO_4 \rightarrow BaSO_4 + H_2S$$

Barium salts can be highly toxic even at low concentrations. Barium carbonate is highly toxic and can be used as rat poison as it readily dissolves in the stomach acid. Barium sulfate is the least toxic barium compound mainly because of its insolubility. Barium sulfate is used in a variety of applications ranging from white paint to X-ray contrast agent.

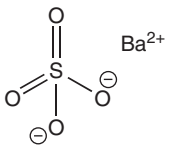

Figure 3.14 *Chemical structure of barium sulfate*

The clinical use of barium sulfate suspension is well known under the term *barium meal*. Patients are given a suspension of barium sulfate to swallow. Using X-ray imaging, the whole oesophagus, the stomach and the intestines can be visualised. Barium sulfate lines the tissue whilst travelling through the digestive tract. The heavy barium ions absorb X-rays readily and therefore these structures become visible in an X-ray screening. Barium sulfate is a well-used and tolerated oral radio-contrast agent. It is also used as radio-contrast agent in enemas (Figure 3.14) [3, 4].

3.6 Exercises

3.6.1 Calcium supplementation

Calcium supplementation is recommended as a dietary supplement especially for menopausal, pregnant or nursing women. There are a variety of calcium salts on the market that can be used for oral administration. For the examples given below, determine the chemical formula, the molecular weight and the Ca^{2+} content (expressed in gram/gram (g/g) and percentage weight/weight (%w/w)).

(a) Calcium carbonate
(b) Calcium lactate
(c) Calcium chloride
(d) Calcium citrate
(e) Calcium gluconate

3.6.2 Complete the redox equation (including the half-equations) and indicate the standard reduction potential assuming that both reaction partners are present in the same concentration.

(a) $Mg + Cl_2 \rightarrow ??$
(b) $Ba + Br_2 \rightarrow ??$

3.6.3 Complete the following redox equation (including the half-equations).

$$Mg + Cl_2 \rightarrow ??$$

Indicate the standard reduction potential assuming a concentration of $[Mg^{2+}] = 0.7\,\text{mol/l}$ and $[Cl^-] = 0.8\,\text{mol/l}$.

3.6.4 Milk of magnesia

Milk of magnesia is typically an 8.7% w/v aqueous suspension of magnesium hydroxide.

(a) What are the chemical formula and the molecular weight of magnesium hydroxide?
(b) What is the concentration of magnesium hydroxide in gram per litre?
(c) How many moles of such magnesium salts are present in a 100-ml suspension?

3.7 Case studies

3.7.1 Magnesium hydroxide suspension

Magnesium hydroxide mixture is an aqueous oral suspension containing hydrated magnesium oxide. It is indicated for use in constipation in adults and children. Typical analysis methods used for quality purposes are based on titration reactions. A certain volume of the suspension containing hydrated magnesium oxide [$Mg(OH)_2$] is typically reacted with a known amount of sulfuric acid (H_2SO_4). The excess acid is then titrated with sodium hydroxide (NaOH) and methyl orange as an indicator [12].

(a) Research the type of titration described. Describe the chemical structure and mode of action of the indicator.
(b) Formulate the relevant chemical equations.
(c) For the analysis, 10 g of the suspension was reacted with 50 ml of 0.5 M H_2SO_4. The excess H_2SO_4 was titrated with 1 M NaOH using methyl orange as indicator. For each titration, the following volume of NaOH has been used:

11.0 ml	11.2 ml	10.9 ml

Calculate the amount of $Mg(OH)_2$ present in your sample. Express your answer in grams and moles.

3.7.2 Calcium carbonate tablets

Your pharmaceutical analysis company has been contacted by an important client and asked to analyse a batch of injections containing calcium carbonate ($CaCO_3$). The description of your brief states that you are supposed to analyse the active pharmaceutical ingredient (API) in these tablets following standard quality assurance guidelines.

Typical analysis methods used for quality purposes are based on titration reactions. A certain amount of the tablet powder is dissolved in water and hydrochloride acid (HCl). A known amount of disodium edetate is added. After adjustment of the pH, the excess disodium edetate is titrated with zinc chloride (ZnCl) using morbant black II solution as indicator [12].

(a) Research the type of titration described. Describe the chemical structure and mode of action of the indicator. You may want to familiarise yourself with chelation (see Section 11.2).
(b) Formulate the relevant chemical equations.
(c) The package states that each tablet contains 1.5 g of $CaCO_3$. For the experiment, 20 tablets are weighed (total weight 42.6 g) and powdered. An amount of powder containing 50 mg of Ca^{2+} is dissolved in water and HCl and reacted with 50 ml of 0.05 M disodium edetate. After adjusting the pH to 10.9, the excess disodium edetate is titrated with 0.05 M $ZnCl_2$ solution. For each titration, the following volume of $ZnCl_2$ has been used:

25.0 ml	24.8 ml	25.3 ml

Calculate the amount of $CaCO_3$ present in your sample. Express your answer in grams and moles.
(d) Critically discuss your result in context with the stated value for the API.
(e) Research the typically accepted error margins.

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