

04-14 Clinical biochemistry and metabolic medicine

14 Clinical biochemistry and metabolic medicine

Clinical biochemistry and metabolic medicine A Mather L Burnett DR Sullivan P Stewart Clinical examination in biochemical and metabolic disorders 346 Biochemical investigations 348 Water and electrolyte homeostasis 349 Sodium homeostasis 349 Functional anatomy and physiology 349 Presenting problems in sodium and water balance 352 Hypovolaemia 352 Hypervolaemia 353 Water homeostasis 355 Functional anatomy and physiology 355 Presenting problems in regulation of osmolality 356 Hyponatraemia 357 Hypernatraemia 358 Potassium homeostasis 360 Functional anatomy and physiology 360 Presenting problems in potassium homeostasis 361 Hypokalaemia 361 Hyperkalaemia 362 Acid-base homeostasis 363 Functional anatomy and physiology 363 Presenting problems in acid-base balance 364 Metabolic acidosis 364 Metabolic alkalosis 366 Respiratory acidosis 367 Respiratory alkalosis 367 Mixed acid-base disorders 367 Calcium homeostasis 367 Magnesium homeostasis 367 Functional anatomy and physiology 367 Presenting problems in magnesium homeostasis 367 Hypomagnesaemia 368 Hypermagnesaemia 368 Phosphate homeostasis 368 Functional anatomy and physiology 368 Presenting problems in phosphate homeostasis 368 Hypophosphataemia 368 Hyperphosphataemia 369 Disorders of amino acid metabolism 369 Disorders of carbohydrate metabolism 370 Disorders of complex lipid metabolism 370 Lipids and lipoprotein metabolism 370 Functional anatomy and physiology 371 Lipids and cardiovascular disease 373 Investigations 373 Presenting problems in lipid metabolism 373 Hypercholesterolaemia 373 Hypertriglyceridaemia 374 Mixed hyperlipidaemia 375 Rare dyslipidaemias 375 Principles of management 375 The porphyrias 378

346 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE Clinical examination in biochemical and metabolic disorders Many biochemical and metabolic disorders are clinically silent or present with non-specific manifestations, and are first detected by laboratory testing. Several abnormalities can be picked up by history and physical examination, however, as summarised below. Insets: (ankle oedema) From Huang H-W, Wong L-S, Lee C-H. Sarcoidosis with bilateral leg lymphedema as the initial presentation: a review of the literature. *Dermatologica Sinica* 2016; 34:29-32; (raised jugular venous pressure) Newby D, Grubb N. *Cardiology: an illustrated colour text*. Edinburgh: Churchill Livingstone, Elsevier Ltd; 2005; (cherry-red spots) Vieira de Rezende Pinto WB, Sgobbi de Souza

PV, Pedroso JL, et al. Variable phenotype and severity of sialidosis expressed in two siblings presenting with ataxia and macular cherry-red spots. J Clin Neurosci 2013; 20:1327–1328; (photosensitive rash) Ferri FF. Ferri's Color atlas and text of clinical medicine. Philadelphia: Saunders, Elsevier Inc.; 2009; courtesy of the Institute of Dermatology, London. Hyperlipidaemia Xanthelasma Corneal arcus Gangliosidosis Cherry-red spot fundus Porphyria Photosensitive rash Hyperlipidaemia Tendon xanthoma Eruptive xanthoma Observation • General appearance • Skin turgor • Oedema • Rash • Eyes Hypervolaemia Raised jugular venous pressure Ankle oedema Hypovolaemia Low blood pressure Rapid pulse Acute hypernatraemia Extra heart sounds Dizziness Delirium Weakness Acute hyponatraemia Cerebral oedema Vomiting Somnolence Seizures Coma Glycogen storage disease Hepatomegaly Abdominal pain Extra heart sounds Atheroma Lung crepitations B C N O P A K L I M J D E F G H H G K N O P D C B A J J L M F I E

Clinical examination in biochemical and metabolic disorders • 347

Assessment of volume status and electrolyte disturbances Check blood pressure, pulse and jugular venous pressure Check for dry mouth Check for sacral and ankle oedema Examine chest for pleural effusion Examine abdomen for hepatomegaly and ascites Check bloods Review results Check ECG Hypokalaemia Hyperkalaemia Check skin turgor Check for signs of hyperlipidaemia Check skin and tendons for xanthomas Check eyes for arcus and xanthelasma Peaked T wave U wave ST depression

348 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE high-speed transport systems (such as pneumatic tubes) and identified with machine-readable labels (such as bar codes). Laboratory instruments have been miniaturised and integrated with robot transport systems to enable multiple rapid analyses of a single sample. Statistical process control techniques are used to assure the quality of analytical results, and increasingly to monitor other aspects of the laboratory, such as the time taken to complete the analysis ('turn-around time'). • Point-of-care testing (POCT) brings selected laboratory analytical systems into clinical areas, to the patient's bedside or even connected to an individual patient. These systems allow the clinician to receive results almost instantaneously for immediate treatment of the patient, although often with lesser precision or at greater cost than using a central laboratory. • The diversity of analyses has widened considerably with the introduction of many techniques borrowed from the chemical or other industries (Box 14.1). Good medical practice involves the appropriate ordering of laboratory investigations and correct interpretation of test results (Box 14.2). The key principles, including the concepts of sensitivity and specificity, are described on page 4. Reference intervals for laboratory results are provided in Chapter 35. Many laboratory investigations can be subject to variability arising from whether the sample is being taken in the fed or fasted state; the timing of sample collection, in relation to diurnal variation of analytes; dosage intervals for therapeutic drug monitoring; sample type, such as serum plasma; use of anticoagulants, such as EDTA, which can interfere with some assays; or artefacts, such as There is a worldwide trend towards increased use of laboratory-based diagnostic investigations, and biochemical investigations in particular. In the health-care systems of developed countries, it has been estimated that 60–70% of all critical decisions taken in regard to patients, and over 90% of data stored in electronic medical records systems, involve a laboratory service or result. This chapter covers a diverse group of disorders affecting adults that are not considered elsewhere in this book, whose primary manifestation is in abnormalities of biochemistry laboratory results, or whose underlying pathophysiology involves disturbance in

specific biochemical pathways. Biochemical investigations There are three broad reasons why a clinician may request a biochemical laboratory investigation: • to screen an asymptomatic subject for the presence of disease • to assist in diagnosis of a patient's presenting complaint • to monitor changes in test results, as a marker of disease progression or response to treatment.

Contemporary medical practice has become increasingly reliant on laboratory investigation and, in particular, on biochemical investigation. This has been associated with extraordinary improvements in the analytical capacity and speed of laboratory instrumentation and the following operational trends:

• Large central biochemistry laboratories feature extensive use of automation and information technology. Specimens are transported from clinical areas to the laboratory using 14.1 Range of analytical modalities used in the clinical biochemistry laboratory Analytical modality Analyte Typical applications Ion-selective electrodes Blood gases, electrolytes (Na, K, Cl) Point-of-care testing (POCT) High-throughput analysers Colorimetric chemical reaction or coupled enzymatic reaction Simple mass or concentration measurement (creatinine, phosphate) Simple enzyme activity High-throughput analysers Ligand assay (usually immunoassay) Specific proteins Hormones Drugs Increasingly available for POCT or high-throughput analysers Chromatography: gas chromatography (GC), highperformance liquid chromatography (HPLC), thin-layer chromatography (TLC) Organic compounds Therapeutic drug monitoring (TDM) Mass spectroscopy (MS) Drug screening (drugs of misuse) Vitamins Biochemical metabolites Spectrophotometry, turbidimetry, nephelometry, fluorimetry Haemoglobin derivatives Specific proteins Immunoglobulins Xanthochromia Lipoproteins Paraproteins Electrophoresis Proteins Some enzymes Paraproteins Isoenzyme analysis Atomic absorption (AA) Inductively coupled plasma/mass spectroscopy (ICP-MS) Trace elements and metals Quantitation of heavy metals Molecular diagnostics Nucleic acid quantification and/or sequence Inherited and somatic cell mutations (Ch. 3) Genetic polymorphisms (Ch. 3) Variations in rates of drug metabolism (Ch. 2) Microbial diagnosis (Ch. 6)

Sodium homeostasis • 349

pump (Na,K-activated adenosine triphosphatase (ATPase)), which is present in all cell membranes. Maintenance of these gradients is essential for many cell processes, including the excitability of conducting tissues such as nerve and muscle. The difference in protein content between the plasma and the interstitial fluid compartment is maintained by the impermeability of the capillary wall to protein. This protein concentration gradient (the colloid osmotic, or oncotic, pressure of the plasma) contributes to the balance of forces across the capillary wall that favour fluid retention within the plasma compartment. The concentration of sodium in the ECF plays a pivotal role in determining plasma osmolality and thereby controlling intracellular volume through changes in water balance between the intracellular and extracellular space. In contrast, plasma volume is largely controlled by total body sodium, which determines volume change. Therefore, disturbances in water homeostasis typically present with biochemical abnormalities such as hyponatraemia or hypernatraemia, whereas disturbances in sodium homeostasis present with hypervolaemia or hypovolaemia as the result of expansion or contraction of ECF volume, respectively. Sodium homeostasis Most of the body's sodium is located in the ECF, where it is by far the most abundant cation. Accordingly, total body sodium is the principal determinant of ECF volume. Sodium intake varies widely between individuals, ranging between 50 and 250 mmol/24 hrs. The kidneys can compensate for these wide variations in sodium intake by increasing excretion of sodium when there is sodium overload, and retaining sodium in the presence of sodium depletion, to maintain

normal ECF volume and plasma volume. Functional anatomy and physiology The functional unit for renal excretion is the nephron (Fig. 14.2). Blood undergoes ultrafiltration in the glomerulus, generating a Fig. 14.1 Normal distribution of body water and electrolytes. Schematic representation of volume (L = litres) and composition (dominant ionic species only shown) of the intracellular fluid (ICF) and extracellular fluid (ECF) in a 70 kg male. The main difference in composition between the plasma and interstitial fluid (ISF) is the presence of appreciable concentrations of protein in the plasma but not the ISF. The Na/K differential is maintained by the Na,K-adenosine triphosphatase (ATPase) pump.

	Intracellular fluid	Interstitial fluid	Plasma
Protein	–	–	–
Extracellular fluid	–	–	–
Cl [–]	–	–	–
HCO ₃ [–]	–	–	–
HPO ₄ ^{2–}	–	–	–
Protein	–	–	–
2K ⁺ + 3Na ⁺ + Na ⁺ + K ⁺	(12 L)	(3 L)	(25 L)

The term urea and electrolytes (U&Es) refers to urea, electrolytes and creatinine. In some countries this is abbreviated to EUC (electrolytes/urea/creatinine).

14.2 How to interpret urea and electrolytes results

Sodium • Largely reflects changes in sodium and water balance • See ‘Hypernatraemia’ and ‘Hyponatraemia’ (pp. 358 and 357) **Potassium** • May reflect K shifts in and out of cells • Low levels usually mean excessive losses (gastrointestinal or renal) • High levels usually mean renal dysfunction • See ‘Hypokalaemia’ and ‘Hyperkalaemia’ (pp. 361 and 362) **Chloride** • Generally changes in parallel with plasma Na • Low in metabolic alkalosis • High in some forms of metabolic acidosis **Bicarbonate** • Abnormal in acid-base disorders • See Box 14.18 (p. 365) **Urea** • Increased with a fall in glomerular filtration rate (GFR), reduced renal perfusion or urine flow rate, and in high protein intake or catabolic states • See page 386 **Creatinine** • Increased with a fall in GFR, in individuals with high muscle mass, and with some drugs • See Fig. 15.2 (p. 387) taking a venous sample proximal to the site of an intravenous infusion. It is therefore important for clinical and laboratory staff to communicate effectively and for clinicians to follow local recommendations concerning collection and transport of samples in the appropriate container and with appropriate labelling.

Water and electrolyte homeostasis Total body water (TBW) is approximately 60% of body weight in an adult male, although the proportion is somewhat more for infants and less for women. In a 70 kg man TBW is therefore about 40 L. Approximately 25 L is located inside cells (the intracellular fluid or ICF), while the remaining 15 L is in the extracellular fluid (ECF) compartment (Fig. 14.1). Most of the ECF (approximately 12 L) is interstitial fluid, which is within the tissues but outside cells, whereas the remainder (about 3 L) is in the plasma compartment. The ion composition between the main body fluid compartments intracellularly and extracellularly is illustrated in Figure 14.1. The dominant positively charged ion (cation) within cells is potassium, whereas phosphates and negatively charged proteins constitute the major intracellular negatively charged ions (anions). In the ECF the dominant cation is sodium, while chloride and, to a lesser extent, bicarbonate are the most important ECF anions. An important difference between the intravascular (plasma) and interstitial compartments of the ECF is that only plasma contains significant concentrations of protein. The major force maintaining the difference in cation concentrations between the ICF and ECF is the sodium–potassium

350 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE Fig. 14.2 The nephron. Letters A–D refer to tubular segments shown in more detail in Figure 14.3. (aa = afferent arteriole; ea = efferent arteriole; md = macula densa) Cortex Medulla A B Thin descending limb Loop of Henle Thin ascending limb Medullary collecting duct Pars recta Proximal (convoluted) tubule Glomerulus C Early distal (convoluted) tubule Late distal tubule Cortical collecting duct D Thick ascending limb aa ea md fluid that is free from cells and protein and which resembles plasma in its electrolyte composition. This is delivered into the renal tubules, where reabsorption of water and various electrolytes occurs. (More detail on the structure and function of the glomerulus is given in Ch. 15.)

The glomerular filtration rate (GFR) is approximately 125 mL/min (equivalent to 180 L/24 hrs) in a normal adult. Over 99% of the filtered fluid is reabsorbed into the blood in the peritubular capillaries during its passage through successive segments of the nephron, largely as a result of tubular reabsorption of sodium. The processes mediating sodium reabsorption, and the factors that regulate it, are key to understanding clinical disturbances and pharmacological interventions of sodium and fluid balance. The nephron can be divided into at least four different functional segments in terms of sodium reabsorption (Fig. 14.3). Proximal renal tubule About 65% of the filtered sodium load is reabsorbed in the proximal renal tubule. The cellular mechanisms are complex but some of the key features are shown in Figure 14.3A. Filtered sodium in the luminal fluid enters the proximal tubular cell through transporters in the apical membrane that couple sodium transport to the entry of glucose, amino acid, phosphate and other organic molecules. Entry of sodium into the tubular cells at this site is also linked to secretion of H^+ ions, through the sodium-hydrogen exchanger (NHE-3). Intracellular H^+ ions are generated within tubular cells from the breakdown of carbonic acid, which is produced from carbon dioxide and water under the influence of carbonic anhydrase. Large numbers of Na,K-ATPase pumps are present on the basolateral membrane of tubular cells, which transport sodium from the cells into the blood. In addition, a large component of the transepithelial flux of sodium, water and other dissolved solutes occurs through gaps between the cells (the 'shunt' pathway). Overall, fluid and electrolyte reabsorption is almost isotonic in this segment, as water reabsorption is matched very closely to sodium fluxes, such that the osmolality of fluid passing into the loop of Henle is very similar to that of plasma. A component of this water flow also passes through the cells, via aquaporin-1 (AQP-1) water channels, which are not sensitive to hormonal regulation. Loop of Henle The thick ascending limb of the loop of Henle (Fig. 14.3B) reabsorbs a further 25% of the filtered sodium but is impermeable to water, resulting in dilution of the luminal fluid. The primary driving force is the Na,K-ATPase on the basolateral cell membrane, but in this segment sodium enters the cell from the lumen through a specific carrier molecule, the Na,K,2Cl co-transporter ('triple co-transporter', or NKCC2), which allows electroneutral entry of these ions into the renal tubular cell by balancing transport of anions (Na^+/K^+) with cations (Cl^-). Some of the potassium accumulated inside the cell recirculates across the apical membrane back into the lumen through a specific potassium channel (ROMK), providing a continuing supply of potassium to match the high concentrations of sodium and chloride in the lumen. A small positive transepithelial potential difference exists in the lumen of this segment relative to the interstitium, and this serves to drive cations such as sodium, potassium, calcium and magnesium between the cells, forming a reabsorptive shunt pathway. Early distal renal tubule About 6% of filtered sodium is reabsorbed in the early distal tubule (also called distal convoluted tubule) (Fig. 14.3C), again driven by the activity of the basolateral Na,K-ATPase. In this segment, entry of sodium into the cell from the luminal fluid occurs through a sodium-chloride co-transport carrier (NCCT). This segment is also impermeable to water, resulting in further dilution of the luminal fluid. There is no significant transepithelial flux of potassium in this segment, but calcium is reabsorbed through the mechanism shown in Figure 14.3C: a basolateral sodium-calcium exchanger leads to low intracellular concentrations of calcium, promoting calcium entry from the luminal fluid through a calcium channel. Late distal renal tubule and collecting ducts The late distal tubule and cortical collecting duct are anatomically and functionally continuous (Fig. 14.3D). Here, sodium entry from the luminal fluid occurs through the epithelial sodium channel (ENaC), generating a substantial lumen-negative transepithelial potential difference. This sodium flux into the tubular cells is balanced by secretion of potassium and hydrogen ions into the lumen and by reabsorption of chloride ions. Potassium is accumulated in the cell by the basolateral Na,K-

ATPase, and passes into the luminal fluid down its electrochemical gradient, through an apical potassium channel (ROMK). Chloride ions pass largely between cells. Hydrogen ion secretion is mediated by an H⁺-ATPase located on the luminal membrane of the intercalated cells, which constitute approximately one-third of the epithelial cells in this segment of the nephron. The distal tubule and collecting duct have a variable permeability to water, depending on circulating levels of vasopressin (antidiuretic hormone, ADH).

Sodium homeostasis • 351

sinus) and the afferent arterioles within the kidney. A further afferent signal is generated within the kidney itself: the enzyme renin is released from specialised smooth muscle cells in the walls of the afferent and efferent arterioles, at the point where they make contact with the early distal tubule (at the macula densa; see Fig. 14.2) to form the juxtaglomerular apparatus. Renin release is stimulated by:

- reduced perfusion pressure in the afferent arteriole
- increased sympathetic nerve activity
- decreased sodium chloride concentration in the distal tubular fluid.

Renin acts on the peptide substrate, angiotensinogen (which is produced by the liver), to produce angiotensin I, which is cleaved by angiotensin-converting enzyme (ACE), largely in the pulmonary capillary bed, to produce angiotensin II (see Fig. 18.18, p. 666). Angiotensin II has multiple actions: it stimulates proximal tubular sodium reabsorption and release of aldosterone from the zona glomerulosa of the adrenal cortex, and causes vasoconstriction of small arterioles. Aldosterone amplifies sodium ion transport processes in this segment are stimulated by the steroid hormone aldosterone, which can increase sodium reabsorption in this segment to a maximum of 2–3% of the filtered sodium load. Less than 1% of sodium reabsorption occurs in the medullary collecting duct, where it is inhibited by atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Regulation of sodium transport

The amount of sodium excreted by the kidney is dependent on the filtered load of sodium (which is largely determined by GFR) and the control of tubular sodium reabsorption. A number of interrelated mechanisms serve to maintain whole-body sodium balance, and hence ECF volume, by matching urinary sodium excretion to sodium intake (Fig. 14.4), and controlling those two processes. Important sensing mechanisms include volume receptors in the cardiac atria and the intrathoracic veins, as well as pressure receptors located in the central arterial tree (aortic arch and carotid Fig. 14.3

Principal transport mechanisms in segments of the nephron. The apical membrane of tubular cells is the side facing the lumen and the basolateral membrane is the side facing the blood. Black circles indicate active transport pumps linked to ATP hydrolysis and white symbols indicate ion channels and transporter molecules. Details of the proportion of sodium reabsorbed, influence of regulatory factors, water permeability and sites of action for different classes of diuretics are shown. The SGLT2 inhibitors are primarily used for the treatment of diabetes but have diuretic properties by blocking SGLT2 in the proximal tubule. At the same site, acetazolamide inhibits carbonic anhydrase (CA), which, by reducing production of hydrogen ions by proximal tubular cells, inhibits sodium–hydrogen exchange through the NHE-3 transporter. Loop diuretics block the NKCC2 transporter in the loop of Henle, whereas thiazide diuretics block the NCCT channel in the early distal tubule. Amiloride and spironolactone block the ENaC channel in the late distal tubule and collecting ducts. See text for further details and abbreviations.

Segment	Transporters/Channels	Diuretics	Water Permeability
Proximal Tubule	SGLT2, NHE-3, Na ⁺ , K ⁺ , Ca ²⁺ , Mg ²⁺	SGLT2 inhibitors, acetazolamide	Highly
Loop of Henle	NKCC2	Loop diuretics	Low
Early distal tubule	NCCT	Thiazide diuretics	Low
Late distal tubule and collecting ducts	ENaC	Amiloride, spironolactone	Variable (ADH)

Legend: Na⁺ Gluc, SGLT2, NHE-3, Na⁺ 'Shunt', 3Na⁺ 2K⁺ CO₂+H₂O HCO₃⁻, H⁺, CA, A Proximal, B Loop of Henle, C Early distal, D Late distal, NKCC2, K⁺, K⁺, Cl⁻, Ca²⁺, Ca²⁺, 3Na⁺, H⁺, HCO₃⁻, Cl⁻, Cl⁻. Principal cell, Intercalated cell. Lumen, Blood, Urine. Na reabsorption (%), hormonal control, Water permeability, Diuretics.

permeable SGLT2 inhibitors Acetazolamide (25%) Impermeable Loop diuretics (6%) Impermeable Thiazide diuretics (2–3%) Aldosterone Permeability increased by vasopressin Amiloride Spironolactone

(65%) Angiotensin II Sympathetic nerves Peritubular forces K^+ ROMK ROMK NCCT

352 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE of sodium-containing fluids or acute blood loss, as summarised in Box 14.4. Pathogenesis Loss of sodium-containing fluid triggers the changes in renal sodium handling and activation of the renin–angiotensin system that were described on page 349. Loss of whole blood, as in acute haemorrhage, is another cause of hypovolaemia, and elicits the same mechanisms for the conservation of sodium and water as loss of sodium-containing fluid. Clinical features Hypovolaemia is primarily a clinical diagnosis, based on characteristic symptoms such as thirst, dizziness and weakness along with characteristic clinical signs (see Box 14.3) in the context of a relevant precipitating illness. Investigations Serum sodium concentrations are usually normal in hypovolaemia. The GFR is usually maintained unless the hypovolaemia is very severe or prolonged, but urinary flow rate is reduced as a consequence of activation of sodium- and water-retaining mechanisms in the nephron. Serum creatinine, which reflects GFR, is usually normal, but serum urea concentration is typically elevated due to a low urine flow rate, which is accompanied retention by its action on the cortical collecting duct. The net effect of activation of the renin–angiotensin system is to raise blood pressure and cause sodium and water retention, thereby correcting hypovolaemia. Changes in GFR alter peritubular hydrostatic pressure and oncotic pressure in opposite directions, resulting in a change in sodium reabsorption. In particular, with hypovolaemia, and a reduction in hydrostatic pressure and an increase in oncotic pressure, there is an increase in sodium reabsorption. The sympathetic nervous system also acts to increase sodium retention, both through haemodynamic mechanisms (afferent arteriolar vasoconstriction and GFR reduction) and by direct stimulation of proximal tubular sodium reabsorption. In contrast, other humoral mediators, such as the natriuretic peptides, which inhibit sodium reabsorption, contribute to natriuresis during periods of sodium and volume excess. Increases in sodium intake cause hypervolaemia, which increases renal perfusion and GFR and suppresses renin production through increased delivery of sodium into the macula densa. This sets in motion a train of events opposite to those that occur in hypovolaemia, to cause an increase in sodium excretion. Presenting problems in sodium and water balance When the balance of sodium intake and excretion is disturbed, any tendency for plasma sodium concentration to change is usually corrected by the osmotic mechanisms controlling water balance (p. 349). As a result, disorders in sodium balance present chiefly as alterations in the ECF volume, resulting in hypovolaemia or hypervolaemia, rather than as an alteration in plasma sodium concentration. Clinical manifestations of altered ECF volume are illustrated in Box 14.3. Hypovolaemia Hypovolaemia is defined as a reduction in circulating blood volume. The most common causes are loss or sequestration Fig. 14.4 Mechanisms involved in the regulation of sodium transport. (ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; ECF = extracellular fluid; GFR = glomerular filtration rate; RAA = renin–angiotensin–aldosterone system; SNS = sympathetic nervous system. $\Uparrow$ indicates an effect to stimulate Na reabsorption and hence reduce Na excretion, while $\Downarrow$ indicates an effect to inhibit Na reabsorption and hence increase Na excretion) • Volume receptors Cardiac atria Intrathoracic veins • Pressure receptors Aortic arch/carotids Afferent arteriole • Tubular fluid [NaCl] Macula densa • Neurohumoral RAA SNS/catecholamines ANP BNP Prostaglandins • Haemodynamic GFR Peritubular forces ECF Na content and volume Afferent

Efferent Sensors Effectors 14.3 Clinical features of hypovolaemia and hypervolaemia Hypovolaemia Hypervolaemia Symptoms Thirst Dizziness on standing Weakness Ankle swelling Abdominal swelling Breathlessness Signs Postural hypotension Tachycardia Dry mouth Reduced skin turgor Reduced urine output Weight loss Delirium, stupor Peripheral oedema Raised JVP Pulmonary crepitations Pleural effusion Ascites Weight gain Hypertension (sometimes) (JVP = jugular venous pressure) 14.4 Causes of hypovolaemia Mechanism Examples Inadequate sodium intake Environmental deprivation, inadequate therapeutic replacement Gastrointestinal sodium loss Vomiting, diarrhoea, nasogastric suction, external fistula Skin sodium loss Excessive sweating, burns Renal sodium loss Diuretic therapy, mineralocorticoid deficiency, tubulointerstitial disease Internal sequestration* Bowel obstruction, peritonitis, pancreatitis, crush injury Reduced blood volume Acute blood loss *A cause of circulatory volume depletion, although total body sodium and water may be normal or increased.

Sodium homeostasis • 353

You would expect that solutions containing plasma proteins (colloids) would be better retained within the vascular space and to be more effective at correcting hypovolaemia than protein-free fluids (crystalloids). However, recent clinical studies have not shown any advantage of giving albumin-containing infusions in the treatment of acute hypovolaemia. Furthermore, synthetic colloids such as dextrans have been shown to be associated with an increased risk of acute kidney injury and mortality in the critically ill. Therefore, crystalloids are the fluid of choice for resuscitation in acute hypovolaemia. More studies, however, are required to clarify the most appropriate crystalloid in this situation, given that normal saline can cause a mild metabolic acidosis, perhaps related to excessive chloride loading, whereas 'balanced solutions', such as Hartmann's, may cause a mild hyponatraemia, as its composition is slightly hypotonic.

Hypervolaemia Hypervolaemia is the result of sodium and water excess and is rare in patients with normal cardiac and renal function, since by increased tubular reabsorption of urea. Similarly, serum uric acid may also rise, reflecting increased reabsorption in the proximal renal tubule. The urine osmolality increases due to increased reabsorption of sodium and water, while the urine sodium concentration falls and sodium excretion may fall to less than 0.1% of the filtered sodium load.

Management Management of sodium and water depletion has two main components: • treat the cause where possible, to stop ongoing salt and water losses • replace the salt and water deficits, and provide ongoing maintenance requirements, usually by intravenous fluid replacement when depletion is severe.

Intravenous fluid therapy Intravenous fluid therapy can be used to maintain water, sodium and potassium intake when the patient is fasting, such as during an acute illness or post-operatively. If any deficits or continuing pathological losses are identified, additional fluid and electrolytes will be required. In prolonged periods of fasting (more than a few days), attention also needs to be given to providing sufficient caloric and nutritional intake to prevent excessive catabolism of body energy stores (p. 704). The daily maintenance requirements for water and electrolytes in a typical adult are shown in Box 14.5 and the composition of some widely available intravenous fluids are given in Box 14.6. The choice of fluid and the rate of administration depend on the clinical circumstances, as assessed at the bedside and from laboratory data, as described in Box 14.7. The choice of intravenous fluid therapy in the treatment of significant hypovolaemia relates to the concepts in Figure 14.1. If fluid containing neither sodium nor protein is given, it will distribute in the body fluid compartments in proportion to the normal distribution of total body water. For example, administration of 1 L of 5% dextrose contributes little (approximately 3/40 of

the infused volume) towards expansion of the plasma volume, which makes this fluid unsuitable for restoring the circulation and perfusion of vital organs. Intravenous infusion of an isotonic (normal) saline solution, on the other hand, is more effective at expanding the ECF, although only a small proportion (about 3/15) of the infused volume actually contributes to plasma volume.

14.5 Basic daily water and electrolyte requirements

Requirement per kg	Typical 70 kg adult
Water	35–45 mL/kg
2.45–3.15 L/24 hrs	
Sodium	1.5–2 mmol/kg
105–140 mmol/24 hrs	
Potassium	1.0–1.5 mmol/kg
70–105 mmol/24 hrs	

14.6 Composition of some isotonic intravenous fluids

Fluid	D-glucose	Calories
Na ⁺ (mmol/L)	CI [−] (mmol/L)	Other (mmol/L)
5% dextrose	50 g	

Normal (0.9%) saline

Hartmann's solution

K⁺ 5 Ca²⁺ 2 Lactate[−] 29

14.7 How to assess fluid and electrolyte balance in hospitalised patients

Step 1: assess clinical volume status

- Examine patient for signs of hypovolaemia or hypervolaemia (see Box 14.3)
- Check daily weight change

Step 2: review fluid balance chart

- Check total volumes IN and OUT on previous day (IN–OUT is positive by ~400 mL in normal balance, reflecting insensible fluid losses of ~800 mL and metabolic water generation of ~400 mL)
- Check cumulative change in daily fluid balance over previous 3–5 days
- Correlate chart figures with weight change and clinical volume status to estimate net fluid balance

Step 3: assess ongoing pathological process

- Check losses from gastrointestinal tract and surgical drains
- Estimate increased insensible losses (e.g. in fever) and internal sequestration ('third space')

Step 4: check plasma U&Es (see Box 14.2)

- Check plasma Na as marker of relative water balance
- Check plasma K as a guide to extracellular K balance
- Check HCO₃[−] as a clue to acid–base disorder
- Check urea and creatinine to monitor renal function

Step 5: prescribe appropriate intravenous fluid replacement therapy

- Replace basic water and electrolytes each day (see Box 14.5)
- Allow for anticipated oral intake and pathological fluid loss
- Adjust amounts of water (if IV, usually given as isotonic 5% dextrose), sodium and potassium according to plasma electrolyte results

354 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE

importance. In Conn's syndrome (p. 674), the pathophysiology also differs, in that increased secretion of aldosterone directly stimulates sodium reabsorption. Clinical features Peripheral oedema is the most common physical sign of hypervolaemia since the excess fluid leaks out of the capillaries to expand the interstitial compartment of the ECF. This is particularly the case in nephrotic syndrome and chronic liver disease, in which hypoalbuminaemia is a prominent feature. The main exception is primary hyperaldosteronism (Conn's syndrome), which presents with hypertension and often hypokalaemia, but in which peripheral oedema is not commonly seen. Investigations Although hypervolaemia is accompanied by an excess of total body sodium, serum sodium concentrations are normal due to the accompanying water retention. Serum concentrations of potassium are normal except in Conn's syndrome, where there is hypokalaemia due to the increased aldosterone production (p. 674). Creatinine, GFR and urea are usually normal, unless the underlying cause of hypervolaemia is renal failure. General investigations may reveal evidence of cardiac, renal or liver disease.

Management The management of hypervolaemia involves a number of components:

- specific treatment directed at the underlying cause, such as ACE inhibitors in heart failure and glucocorticoids in minimal change nephropathy
- restriction of dietary sodium (to 50–80 mmol/24 hrs) to match the diminished excretory capacity
- treatment with diuretics. Diuretic therapy

Diuretics play a pivotal role in the treatment of hypervolaemia due to salt and water retention and in hypertension (p. 513). They act by inhibiting sodium reabsorption at various locations along the nephron (see Fig. 14.3). Their potency and adverse effects relate to their mechanism and site of action. Carbonic anhydrase inhibitors Acetazolamide is a carbonic anhydrase inhibitor that inhibits intracellular production of H^+ ions in the proximal tubule, reducing the fraction of sodium reabsorption that is exchanged for H^+ by the apical membrane sodium-hydrogen exchanger. It is a weak diuretic but is seldom used clinically for this purpose, since only a small fraction of proximal sodium reabsorption uses this mechanism, and much of the sodium that is not reabsorbed in the proximal tubule can be reabsorbed by downstream segments of the nephron. Sodium-dependent glucose transporter inhibitors Inhibitors of the sodium-dependent glucose transporter 2 (SGLT2), such as dapagliflozin and canagliflozin, simultaneously block glucose and sodium reabsorption in the proximal tubule. They have mild diuretic properties but are principally used to lower blood glucose in the treatment of diabetes (p. 745). Loop diuretics Loop diuretics, such as furosemide, inhibit sodium reabsorption in the thick ascending limb of the loop of Henle, by blocking the action of the apical membrane NKCC2 co-transporter. Because this segment reabsorbs a large fraction the kidney has a large capacity to increase renal excretion of sodium and water via the homeostatic mechanisms described on page 349. Pathogenesis The most common systemic disorders responsible for hypervolaemia are outlined in Box 14.8. In cardiac failure, cirrhosis and nephrotic syndrome, sodium retention occurs in response to circulatory insufficiency caused by the primary disorder, as illustrated in Figure 14.5. The pathophysiology is different in renal failure, when the primary cause of volume expansion is the profound reduction in GFR impairing sodium and water excretion, while secondary tubular mechanisms are of lesser 14.8 Causes of sodium and water excess Mechanism Examples Impaired renal function Primary renal disease Primary hyperaldosteronism* Conn's syndrome Secondary hyperaldosteronism (see Fig. 14.5) Congestive cardiac failure Cirrhotic liver disease Nephrotic syndrome Protein-losing enteropathy Malnutrition Idiopathic/cyclical oedema Renal artery stenosis* *Conditions in this box other than primary hyperaldosteronism and renal artery stenosis are typically associated with generalised oedema. Fig. 14.5 Secondary mechanisms causing sodium excess and oedema in cardiac failure, cirrhosis and nephrotic syndrome. Primary renal retention of Na and water may also contribute to oedema formation when glomerular filtration rate is significantly reduced (see Box 14.8 and p. 395). Cirrhosis Nephrotic syndrome Heart failure Peripheral vasodilatation/ splanchnic pooling Reduced albumin synthesis Heavy proteinuria ↓ Cardiac output ↓ Plasma albumin ↓ Arterial filling • ↑ Renin-angiotensin-aldosterone • ↑ Renal sympathetic drive • Altered renal haemodynamics ↑ Venous pressure Na^+ + H_2O retention ↑ Capillary hydrostatic pressure ↓ Capillary oncotic pressure Oedema

Water homeostasis • 355

An important feature of the most commonly used diuretic drugs (furosemide, thiazides and amiloride) is that they act on their target molecules from the luminal side of the tubular epithelium. Since they are highly protein-bound in the plasma, very little reaches the urinary fluid by glomerular filtration, but there are active transport mechanisms for secreting organic acids and bases, including these drugs, across the proximal tubular wall into the lumen, resulting in adequate drug concentrations being delivered to later tubular segments. This secretory process may be impaired by certain other drugs, and also by accumulated organic anions as occurs in chronic kidney disease and chronic liver failure, leading to resistance to diuretics. Diuretic resistance is

encountered under a variety of circumstances, including impaired renal function, activation of sodium-retaining mechanisms, impaired oral bioavailability (such as in patients with gastrointestinal disease) and decreased renal blood flow. In these circumstances, short-term intravenous therapy with a loop-acting agent such as furosemide may be useful. Combinations of diuretics administered orally may also increase potency. Either a loop or a thiazide drug can be combined with a potassium-sparing drug, and all three classes can be used together for short periods, with carefully supervised clinical and laboratory monitoring.

Water homeostasis Daily water intake can vary from about 500 mL to several litres a day. About 800 mL of water is lost daily through the stool, sweat and the respiratory tract (insensible losses) and about 400 mL is generated daily through oxidative metabolism (metabolic water). The kidneys are chiefly responsible for adjusting water excretion to balance intake, endogenous production and losses so as to maintain total body water content and serum osmolality within the reference range of 280–296 mOsmol/kg.

Functional anatomy and physiology While regulation of total ECF volume is largely achieved through renal control of sodium excretion, mechanisms exist to allow for the excretion of urine that is hypertonic or hypotonic in relation to plasma to maintain constant plasma osmolality. These functions are largely achieved by the loop of Henle and the collecting ducts (see Fig. 14.2). The countercurrent configuration of flow in adjacent limbs of the loop (Fig. 14.6) involves osmotic movement of water from the descending limbs and reabsorption of the filtered sodium, these drugs are potent diuretics, and are commonly used in diseases associated with significant oedema. Loop diuretics cause excretion not only of sodium (and with it water) but also of potassium. This occurs largely as a result of delivery of increased amounts of sodium to the late distal tubule and cortical collecting ducts, where sodium reabsorption is associated with excretion of potassium, and is amplified if circulating aldosterone levels are high.

Thiazide diuretics Thiazide diuretics inhibit sodium reabsorption in the early distal tubule, by blocking the NCCT co-transporter in the apical membrane. Since this segment reabsorbs a much smaller fraction of the filtered sodium, these are less potent than loop diuretics, but are widely used in the treatment of hypertension and less severe oedema. Like loop diuretics, thiazides increase excretion of potassium through delivery of increased amounts of sodium to the late distal tubule and collecting duct. They are the diuretics that are most likely to be complicated by the development of hyponatraemia, as outlined on page 357.

Potassium-sparing diuretics Potassium-sparing diuretics act on the late distal renal tubule and cortical collecting duct segment to inhibit sodium reabsorption. Since sodium reabsorption and potassium secretion are linked at this site, the reduced sodium reabsorption is accompanied by reduced potassium secretion. The apical sodium channel (see Fig. 14.3) is blocked by amiloride and triamterene, while spironolactone and eplerenone also act at this site by blocking binding of aldosterone to the mineralocorticoid receptor.

Osmotic diuretics These act independently of a specific transport mechanism. As they are freely filtered at the glomerulus but not reabsorbed by any part of the tubular system, they retain fluid osmotically within the tubular lumen and limit the extent of sodium reabsorption in multiple segments. Mannitol is the most commonly used osmotic diuretic. It is given by intravenous infusion to achieve short-term diuresis in conditions such as cerebral oedema.

Clinical use of diuretics The following principles should be observed when using diuretics:

- Use the minimum effective dose.
- Use for as short a period of time as necessary.
- Monitor regularly for adverse effects.

The choice of diuretic is determined by the potency required, the presence of coexistent conditions, and the side-effect profile. Adverse effects encountered with the most frequently used classes of diuretic (loop drugs and thiazide drugs) are summarised in Box 14.9. Volume depletion and electrolyte disorders are the most common, as predicted from their mechanism of action. The metabolic side-

effects listed are rarely of clinical significance and may reflect effects on K⁺ channels that influence insulin secretion (p. 723). Since most drugs from these classes are sulphonamides, there is a relatively high incidence of hypersensitivity reactions, and occasional idiosyncratic side-effects in a variety of organ systems. The side-effect profile of the potassium-sparing diuretics differs in a number of important respects from that of other diuretics. The disturbances in potassium, magnesium and acid-base balance are in the opposite direction, so that normal or increased levels of potassium and magnesium are found in the blood, and there is a tendency to metabolic acidosis, especially when renal function is impaired.

14.9 Adverse effects of loop-acting and thiazide diuretics

Renal side-effects • Hypovolaemia • Hyponatraemia • Hypokalaemia • Metabolic alkalosis • Hyperuricaemia • Hypomagnesaemia • Hypercalciuria (loop) • Hypocalciuria (thiazide)

Metabolic side-effects • Glucose intolerance/ hyperglycaemia • Hyperlipidaemia

Miscellaneous side-effects • Hypersensitivity reactions • Erectile dysfunction • Acute pancreatitis/cholecystitis (thiazides)

356 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE

osmolality approaching that in the medullary tip (up to 1200 mOsmol/kg). Parallel to these changes in vasopressin release are changes in water-seeking behaviour triggered by the sensation of thirst, which also becomes activated as plasma osmolality rises. In summary, for adequate dilution of the urine there must be:

- adequate solute delivery to the loop of Henle and early distal tubule
- normal function of the loop of Henle and early distal tubule
- absence of vasopressin in the circulation.

If any of these processes is faulty, water retention and hyponatraemia may result. Conversely, to achieve concentration of the urine there must be:

- adequate solute delivery to the loop of Henle
- normal function of the loop of Henle
- vasopressin release into the circulation
- vasopressin action on the collecting ducts.

Failure of any of these steps may result in inappropriate water loss and hypernatraemia. Presenting problems in regulation of osmolality

Changes in plasma osmolality are largely determined by changes in serum sodium concentration and its associated anions. Changes in sodium concentration usually occur because of disturbances in water balance either because there is a relative excess of body water compared to total body sodium (hyponatraemia) or solute from neighbouring ascending limbs, to set up a gradient of osmolality from isotonic (like plasma) in the renal cortex to hypertonic (around 1200 mOsmol/kg) in the inner part of the medulla. At the same time, the fluid emerging from the thick ascending limb is hypotonic compared to plasma because it has been diluted by the reabsorption of sodium, but not water, from the thick ascending limb and is further diluted in the early distal tubule. As this dilute fluid passes from the cortex through the collecting duct system to the renal pelvis, it traverses the medullary interstitial gradient of osmolality set up by the operation of the loop of Henle, and water is able to be reabsorbed. Further changes in the urine osmolality on passage through the collecting ducts depend on the circulating level of vasopressin, which is released by the posterior pituitary gland under conditions of increased plasma osmolality or hypovolaemia (p. 688).

- When water intake is high and plasma osmolality is normal or low-normal (Fig. 14.6B), vasopressin levels are suppressed and the collecting ducts remain impermeable to water. The luminal fluid osmolality remains low, resulting in the excretion of a dilute urine (minimum osmolality approximately 50 mOsmol/kg in a healthy young person).
- When water intake is restricted and plasma osmolality is high (Fig. 14.6A), or in the presence of plasma volume depletion, vasopressin levels rise. This causes water permeability of the collecting ducts to increase through binding of vasopressin to the V₂ receptor, which enhances collecting duct water permeability through the insertion of AQP-2 channels into the luminal cell membrane. This results in osmotic reabsorption of water along the entire length of the collecting duct, with maximum urine

Fig. 14.6 Mechanisms of renal water handling. (1) Filtrate from

the proximal tubule is isosmotic to plasma and cortical interstitial fluid. (2) Water moves down its osmotic gradient, concentrating the filtrate but not diluting the interstitium, as the vasa recta carries away the water. (3) The filtrate is at its highest concentration at the bend of the loop and therefore the surrounding medulla is also concentrated. (4) NaCl is pumped out of the filtrate in the thick ascending limb and early distal tubule, increasing the interstitial fluid osmolality. (5) The filtrate has a concentration of 100 mOsmol/kg as it leaves the early distal tubule. A In the face of water deficit, vasopressin causes water permeability of the collecting ducts, resulting in osmotic reabsorption of water. B In the situation of water overload, vasopressin secretion is suppressed and urine remains dilute. A Loop of Henle Passive diffusion of H₂O Active transport of NaCl Portions of tubule impermeable to H₂O Permeability to H₂O increased by vasopressin Vasa recta From proximal tubule Blood flow Blood flow

H₂O NaCl NaCl NaCl H₂O H₂O H₂O H₂O H₂O

•
Distal tubule Distal tubule

Water deficit B Water overload Cortex Medulla Collecting tubule

Water homeostasis • 357

euvolaemic, with no evidence of cardiac, renal or hepatic disease potentially associated with hyponatraemia. Other non-osmotic stimuli that cause release of vasopressin (pain, stress, nausea) should also be excluded. Supportive laboratory findings are shown in Box 14.11. Hyponatraemia with hypervolaemia In this situation, excess water retention is associated with sodium retention and volume expansion, as in heart failure, liver disease or kidney disease. Clinical features Hyponatraemia is often asymptomatic but can also be associated with profound disturbances of cerebral function, manifesting as anorexia, nausea, vomiting, delirium, lethargy, seizures and coma. The likelihood of symptoms occurring is related to the speed at which hyponatraemia develops rather than the severity of hyponatraemia. This is because water rapidly flows into cerebral cells when plasma osmolality falls acutely, causing them to become swollen and ischaemic. However, when hyponatraemia develops gradually, cerebral neurons have time to respond by reducing intracellular osmolality, through excreting potassium and reducing synthesis of intracellular organic osmolytes (Fig. 14.7). The osmotic gradient favouring water movement into the cells is thus reduced and symptoms are avoided. This process takes about 24–48 hours and hyponatraemia is therefore classified as acute (< 48 hours) and chronic (> 48 hours). Hyponatraemia can also be defined as mild (130–135 mmol/L), moderate (125–129 mmol/L) or severe (< 124 mmol/L), based on biochemical findings or on the degree of severity of symptoms (Box 14.12). Investigations An algorithm for the clinical assessment of patients with hyponatraemia is shown in Figure 14.8. Artefactual causes of hyponatraemia should be considered in all cases. These include severe hyperlipidaemia or hyperproteinaemia, when the aqueous fraction of the serum specimen is reduced because of the volume occupied by the macromolecules (although this artefact is dependent on the assay technology). Transient hyponatraemia a relative lack of body water compared to total body sodium (hypernatraemia). Abnormalities of water balance can result from disturbances in urinary concentration or dilution. If extracellular osmolality falls abruptly, water flows rapidly across cell membranes, causing cell swelling, whereas cell shrinkage occurs

when osmolality rises. Cerebral function is particularly sensitive to such volume changes, particularly brain swelling during hypo-osmolality, which can lead to an increase in intracerebral pressure and reduced cerebral perfusion.

Hyponatraemia Hyponatraemia is defined as a serum Na < 135 mmol/L. It is a common electrolyte abnormality with many potential underlying causes, as summarised in Box 14.10.

Pathophysiology In all cases, hyponatraemia is caused by greater retention of water relative to sodium. The causes are best categorised according to associated changes in the ECF volume (Box 14.10).

Hyponatraemia with hypovolaemia In this situation there is depletion of sodium and water but the sodium deficit exceeds the water deficit, causing hypovolaemia and hyponatraemia (see Box 14.3). The cause of sodium loss is usually apparent and common examples are shown in Box 14.10.

Hyponatraemia with euvolaemia In this situation there are no major disturbances of body sodium content and the patient is clinically euvolaemic. Excess body water may be the result of abnormally high intake, either orally (primary polydipsia) or as a result of medically infused fluids (as intravenous dextrose solutions, or by absorption of sodium-free bladder irrigation fluid after prostatectomy). Water retention also occurs in the syndrome of inappropriate secretion of antidiuretic hormone, or vasopressin (SIADH). In this condition, an endogenous source of vasopressin (either cerebral or tumour-derived) promotes water retention by the kidney in the absence of an appropriate physiological stimulus (Box 14.11). The clinical diagnosis requires the patient to be

14.10 Causes of hyponatraemia

Volume status

Examples

Hypovolaemic Renal sodium losses: Diuretic therapy (especially thiazides) Adrenocortical failure
Gastrointestinal sodium losses: Vomiting Diarrhoea Skin sodium losses: Burns

Euvolaemic Primary polydipsia Excessive electrolyte-free water infusion SIADH Hypothyroidism

Hypervolaemic Congestive cardiac failure Cirrhosis Nephrotic syndrome Chronic kidney disease (during free water intake) (SIADH = syndrome of inappropriate antidiuretic hormone (vasopressin) secretion; see Box 14.11).

14.11 Causes and diagnosis of syndrome of inappropriate antidiuretic hormone secretion

Causes • Tumours • Central nervous system disorders: stroke, trauma, infection, psychosis, porphyria • Pulmonary disorders: pneumonia, tuberculosis, obstructive lung disease • Drugs: anticonvulsants, psychotropics, antidepressants, cytotoxics, oral hypoglycaemic agents, opiates • Idiopathic

Diagnosis • Low plasma sodium concentration (typically < 130 mmol/L) • Low plasma osmolality (< 275 mOsmol/kg) • Urine osmolality not minimally low (typically > 100 mOsmol/kg) • Urine sodium concentration not minimally low (> 30 mmol/L) • Low-normal plasma urea, creatinine, uric acid • Clinical euvolaemia • Absence of adrenal, thyroid, pituitary or renal insufficiency • No recent use of diuretics • Exclusion of other causes of hyponatraemia (see Box 14.10) • Appropriate clinical context (above)

358 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE Fig. 14.7 Hyponatraemia and the brain. Numbers represent osmolality (osmo) in mOsmol/kg. Acute hyponatraemia Slowly developing hyponatraemia Normal cerebral cell Plasma osmo

Osmo

Osmo

Osmo

H₂O H₂O Loss of cellular osmolytes Osmo

Cerebral swelling → cerebral oedema Osmo

Plasma osmo

No change in cerebral cell size Plasma osmo falls abruptly 290→220 Plasma osmo falls gradually 290→220

Symptoms and severity of hyponatraemia	Severity	Serum sodium	Symptoms
Mild	130–135 mmol/L	None	Moderate
125–129 mmol/L	Nausea	Delirium	Headache
Severe < 124 mmol/L	Vomiting	Somnolence	Seizures
Coma	Cardiorespiratory arrest		

may also occur due to osmotic shifts of water out of cells during hyperosmolar states caused by acute hyperglycaemia or by mannitol infusion, but in these cases plasma osmolality is normal. When these conditions have been excluded, serum and urine electrolytes and osmolality (Fig. 14.8) are usually the only tests required to clarify the underlying cause. Hypovolaemic hyponatraemia is characterised by a low urinary sodium concentration (< 30 mmol/L) when there are extrarenal causes of sodium loss and high urinary sodium concentration (> 30 mmol/L) in patients with excessive renal sodium loss. Measurement of vasopressin is not generally helpful in distinguishing between different categories of hyponatraemia. This is because concentrations of vasopressin are raised both in hypovolaemic states and in most chronic hypervolaemic states, as the impaired circulation in those disorders activates vasopressin release through non-osmotic mechanisms. Indeed, patients with these disorders may have higher circulating vasopressin (ADH) levels than patients with SIADH. The only disorders listed in Box 14.10 in which vasopressin is suppressed are primary polydipsia and iatrogenic water intoxication, where the hypo-osmolar state inhibits vasopressin release from the pituitary.

Management The treatment of hyponatraemia is critically dependent on its rate of development, severity, presence of symptoms and underlying cause. If hyponatraemia has developed rapidly (< 48 hours) and there are signs of cerebral oedema, such as obtundation or convulsions, sodium levels should be restored rapidly to normal by infusion of hypertonic (3%) sodium chloride. A common approach is to give an initial bolus of 150 mL over 20 minutes, which may be repeated once or twice over the initial hours of observation, depending on the neurological response and rise in plasma sodium. Rapid correction of hyponatraemia that has developed more slowly (> 48 hours) can be hazardous, since brain cells adapt to slowly developing hypo-osmolality by reducing the intracellular osmolality, thus maintaining normal cell volume (see Fig. 14.7). Under these conditions, an abrupt increase in extracellular osmolality can lead to water shifting out of neurons, abruptly reducing their volume and causing them to detach from their myelin sheaths. The resulting 'myelinolysis' can produce permanent structural and functional damage to mid-brain structures, and is generally fatal. The rate of correction of the plasma Na concentration in chronic asymptomatic hyponatraemia should not exceed 10 mmol/L/24 hrs, and an even slower rate is generally safer. The underlying cause should also be treated. For hypovolaemic patients, this involves controlling the source of sodium loss, and administering intravenous saline if clinically warranted. Patients with euvolaemic hyponatraemia generally respond to fluid restriction in the range of 600–1000 mL/24 hrs, accompanied where possible by withdrawal of the precipitating stimulus (such as drugs causing SIADH). In patients with persistent hyponatraemia due to prolonged SIADH, oral urea therapy (30–45 g/day) can be used, which provides a solute load to promote water excretion. Oral vasopressin receptor antagonists such as tolvaptan may also be used to block the vasopressin-mediated component of water retention in a range of hyponatraemic conditions, but concerns exist with regard to the risk of overly rapid correction of hyponatraemia with these agents. Hypervolaemic patients with hyponatraemia need treatment of the underlying condition, accompanied by cautious use of diuretics in conjunction with strict fluid restriction.

Potassium-sparing diuretics may be particularly useful in this context when there is significant secondary hyperaldosteronism. Hyponatraemia Hyponatraemia is defined as existing when the serum Na is

“ 145 mmol/L. The causes are summarised in Box 14.13, grouped according to any associated disturbance in total body sodium content. Pathophysiology Hyponatraemia occurs due to inadequate concentration of the urine in the face of restricted water intake. This can arise because

Water homeostasis • 359

of failure to generate an adequate medullary concentration gradient in the kidney due to low GFR or loop diuretic therapy, but more commonly is caused by failure of the vasopressin system. This can occur because of pituitary damage (cranial diabetes insipidus, p. 687) or because the collecting duct cells are unable to respond to circulating vasopressin concentrations in the face of restricted water intake (nephrogenic diabetes insipidus). Whatever the underlying cause, sustained or severe hyponatraemia generally reflects an impaired thirst mechanism or responsiveness to thirst. Clinical features Patients with hyponatraemia generally have reduced cerebral function, either as a primary problem or as a consequence of the hyponatraemia itself, which results in dehydration of neurons and brain shrinkage. In the presence of an intact thirst mechanism and preserved capacity to obtain and ingest water, Fig. 14.8 Algorithm for the diagnosis of hyponatraemia. (ECF = extracellular fluid; SIADH = syndrome of inappropriate antidiuretic hormone (vasopressin) secretion) Low serum sodium (<135mmol/L) Check urine osmolality Excessive water intake Measure urine sodium Normal Abnormal <100mOsmol/kg

“ 100mOsmol/kg Low intravascular volume Evidence of kidney disease? < 30mmol/L 30mmol/L Vomiting Diarrhoea Pancreatitis Cirrhosis Heart failure Nephrotic syndrome Check for evidence of hypovolaemia Signs of volume depletion? Signs of fluid overload? Signs of hypovolaemia Normal ECF volume Diuretics Adrenal insufficiency SIADH Hypothyroidism Check urea, glucose, lipids, immunoglobins Hypotonic hyponatraemia (osmolality <275mOsmol/kg) Primary polydipsia Beer potomania Low solute intake Consider non-hypotonic hyponatraemia Yes No Hyponatraemia may be secondary to kidney disease Investigate and treat underlying disorder 14.13 Causes of hyponatraemia Volume status Examples Hypovolaemic Renal sodium losses: Diuretic therapy (especially osmotic diuretic, or loop diuretic during water restriction) Glycosuria (hyperglycaemic hyperosmolar state, p. 738) Gastrointestinal sodium losses: Colonic diarrhoea Skin sodium losses: Excessive sweating Euvolaemic Diabetes insipidus (central or nephrogenic) (p. 687) Hypervolaemic Enteral or parenteral feeding Intravenous or oral salt administration Chronic kidney disease (during water restriction)

360 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE the urine occurs in the late distal tubule and cortical collecting duct to ensure that the amount removed from the blood is proportional to the ingested load. The mechanism for potassium secretion in the distal parts of the nephron is shown in Figure 14.3D. Movement of potassium from blood to lumen is dependent on active uptake across the basal cell membrane by the Na,K-ATPase, followed by diffusion of potassium through the ROMK channel into the tubular fluid. The electrochemical gradient for potassium movement into the lumen is contributed to both by the high intracellular potassium concentration and by the negative luminal potential difference relative to the blood. A number of factors influence the rate of potassium secretion. Luminal influences include the rate of sodium delivery and fluid flow through the late distal tubule and cortical collecting ducts. This is a major factor responsible for the increased potassium loss that accompanies diuretic treatment. Agents interfering with the generation of the negative luminal potential also impair potassium secretion, and this is the basis of reduced potassium secretion associated with potassium-sparing diuretics such as amiloride. Factors acting on the blood side of this tubular segment include plasma potassium and pH, such that hyperkalaemia and alkalosis both enhance potassium secretion directly. However, the most important factor in the acute and chronic adjustment of potassium secretion to match metabolic potassium load is aldosterone. As shown in Figure 14.9, a negative feedback relationship exists between the plasma potassium concentration and aldosterone. In addition to its regulation by the renin-angiotensin system (see Fig. 18.18, p. 666), aldosterone is released from the adrenal cortex in direct response to an elevated plasma potassium. Aldosterone then acts on the kidney to enhance potassium secretion, hydrogen secretion and sodium reabsorption, in the late distal tubule and cortical collecting ducts. The resulting increased excretion of potassium maintains plasma potassium within a narrow range (3.6–5.0 mmol/L). Factors that reduce angiotensin II levels may indirectly affect potassium balance by blunting the rise in aldosterone that would otherwise be provoked by hyperkalaemia. This accounts for the increased risk of hyperkalaemia during therapy with ACE inhibitors and related drugs.

Fig. 14.9 Feedback control of plasma potassium concentration. Kidney ↑K⁺ excretion Adrenal cortex (Zona glomerulosa) ↑ Plasma [K⁺] ↓ Plasma [K⁺] ↑K⁺ intake Negative feedback ↑Aldosterone

hypernatraemia may not progress very far. If adequate water is not obtained, dizziness, delirium, weakness and, ultimately, coma and death can result. Management Treatment of hypernatraemia depends on both the rate of development and the underlying cause. If there is reason to think that the condition has developed rapidly, neuronal shrinkage may be acute and relatively rapid correction may be attempted. This can be achieved by infusing an appropriate volume of intravenous fluid (isotonic 5% dextrose or hypotonic 0.45% saline) at an initial rate of 50–70 mL/hr. In older, institutionalised patients, however, it is more likely that the disorder has developed slowly, and extreme caution should be exercised in lowering plasma sodium to avoid the risk of cerebral oedema. Where possible, the underlying cause should also be addressed (Box 14.13). Elderly patients are predisposed, in different circumstances, to both hyponatraemia and hypernatraemia, and a high index of suspicion of these electrolyte disturbances is appropriate in elderly patients with recent alterations in behaviour (Box 14.14).

Potassium homeostasis Potassium is the major intracellular cation (see Fig. 14.1), and the steep concentration gradient for potassium across the cell membrane of excitable cells plays an important part in generating the resting membrane potential and allowing the propagation of the action potential that is crucial to normal functioning of nerve, muscle and cardiac tissues. Control of body potassium balance is described below.

Functional anatomy and physiology The kidneys normally excrete some 90% of the daily intake of potassium, typically 80–100 mmol/24 hrs. Potassium is freely filtered at the glomerulus; around 65% is reabsorbed in the proximal tubule and

a further 25% in the thick ascending limb of the loop of Henle. Little potassium is transported in the early distal tubule but a significant secretory flux of potassium into 14.14 Hyponatraemia and hypernatraemia in old age • Decline in GFR: older patients are predisposed to both hyponatraemia and hypernatraemia, mainly because, as glomerular filtration rate declines with age, the capacity of the kidney to dilute or concentrate the urine is impaired. • Hyponatraemia: occurs when free water intake continues in the presence of a low dietary salt intake and/or diuretic drugs (particularly thiazides). • Vasopressin release: water retention is aggravated by any condition that stimulates vasopressin release, especially heart failure. Moreover, the vasopressin response to non-osmotic stimuli may be brisker in older subjects. Appropriate water restriction may be a key part of management. • Hypernatraemia: occurs when water intake is inadequate, due to physical restrictions preventing access to drinks and/or blunted thirst. Both are frequently present in patients with advanced dementia or following a severe stroke. • Dietary salt: hypernatraemia is aggravated if dietary supplements or medications with a high sodium content (especially effervescent preparations) are administered. Appropriate prescription of fluids is a key part of management.

Potassium homeostasis • 361

Pathophysiology Hypokalaemia is generally indicative of abnormal potassium loss from the body, through either the kidney or the gastrointestinal tract. Renal causes of hypokalaemia can be divided into those with and those without hypertension. Hypokalaemia in the presence of hypertension may be due to increased aldosterone secretion in Conn's syndrome (p. 674) or a genetic defect affecting sodium channels in the distal nephron (Liddle's syndrome). Excessive intake of liquorice or treatment with carbenoxolone may result in a similar clinical picture, due to inhibition of the renal 11 β HSD2 enzyme, which inactivates cortisol in peripheral tissues. If blood pressure is normal or low, hypokalaemia can be classified according to the associated change in acid-base balance. Inherited defects in tubular transport should be suspected when hypokalaemia occurs in association with alkalosis, provided that diuretic use has been excluded. One such disease is Bartter's syndrome, in which sodium reabsorption in the thick ascending limb of Henle is defective, usually due to a loss-of-function mutation of the NKCC2 transporter. The clinical and biochemical features are similar to those in chronic treatment with furosemide. In Gitelman's syndrome there is a loss-of-function mutation affecting the NCCT transporter in the early distal tubule. The clinical and biochemical features are similar to chronic thiazide treatment. Note that while both Bartter's and Gitelman's syndromes are characterised by hypokalaemia and hypomagnesaemia, urinary calcium excretion is increased in Bartter's syndrome but decreased in Gitelman's syndrome, analogous to the effects of the loop and thiazide diuretics, respectively, on calcium transport (see Box 14.9). If hypokalaemia occurs in the presence of a normal blood pressure and metabolic acidosis, renal tubular acidosis (proximal or 'classical' distal) should be suspected (p. 364). When hypokalaemia is due to potassium wasting through the gastrointestinal tract, the cause is usually obvious clinically. In some cases, when there is occult induction of vomiting, the hypokalaemia is characteristically associated with metabolic alkalosis, due to loss of gastric acid. If, however, potassium loss has occurred through the surreptitious use of aperients, the hypokalaemia is generally associated with metabolic acidosis. In both cases, urinary potassium excretion is low unless there is significant extracellular volume depletion, which can raise urinary potassium levels by stimulating aldosterone production. Hypokalaemia can also be caused by redistribution of potassium into cells as the result of insulin, β -adrenoceptor agonists and alkalosis,

or as the result of K⁺ flux into muscle in hypokalaemic periodic paralysis, which is associated with mutations in several genes that regulate transmembrane ion flow into muscle cells. Finally, reduced dietary intake of potassium can contribute to hypokalaemia but is seldom the only cause, except in extreme cases. Clinical features Patients with mild hypokalaemia (plasma K⁺ 3.0–3.3 mmol/L) are generally asymptomatic, but more profound reductions in plasma potassium often lead to muscular weakness and associated tiredness. Ventricular ectopic beats or more serious arrhythmias may occur and the arrhythmogenic effects of digoxin may be potentiated. Typical electrocardiogram (ECG) changes occur, affecting the T wave in particular (p. 347). Functional bowel obstruction may occur due to paralytic ileus. Long-standing hypokalaemia may cause renal tubular damage (hypokalaemic nephropathy) and can interfere with the tubular response to vasopressin (acquired nephrogenic diabetes insipidus), resulting in polyuria and polydipsia.

Presenting problems in potassium homeostasis Changes in the distribution of potassium between the ICF and ECF compartments can alter plasma potassium concentration, without any overall change in total body potassium content. Potassium is driven into the cells by extracellular alkalosis and by a number of hormones, including insulin, catecholamines (through the β_2 -receptor) and aldosterone. Any of these factors can produce hypokalaemia, whereas extracellular acidosis, lack of insulin, and insufficiency or blockade of catecholamines or aldosterone can cause hyperkalaemia due to efflux of potassium from the intracellular compartment. Hypokalaemia Hypokalaemia is a common electrolyte disturbance and is defined as existing when serum K⁺ falls below 3.5 mmol/L. The main causes of hypokalaemia are shown in Box 14.15. } } } } } Cause Other features and comment

Reduced intake	Urine K ⁺ > 20–30 mmol/24 hrs	Dietary deficiency	Potassium-free intravenous fluids	Redistribution into cells	Alkalosis	Insulin	Catecholamines	β -adrenergic agonists
Hypokalaemic periodic paralysis	Caused by flux of K ⁺ into cells	Increased urinary excretion	Urine K ⁺ > 20–30 mmol/24 hrs	Activation of mineralocorticoid receptor: Conn's syndrome	Cushing's syndrome	Glucocorticoid excess	Carbenoxelone/liquorice	Associated with hypertension and alkalosis
Genetic disorders: Liddle's syndrome	Bartter's syndrome	Gitelman's syndrome	Renal tubular acidosis Type 1 (distal)	Type 2 (proximal)	Associated with hypertension and alkalosis	Associated with hypertension, alkalosis and hypomagnesaemia	Inherited and acquired forms; associated with high serum chloride.	Type 2 associated with glycosuria, aminoaciduria and phosphaturia
Acetazolamide	Associated with acidosis	Diuresis: Loop diuretics	Thiazides	Recovery from acute tubular necrosis	Recovery from renal obstruction	Increased sodium delivery to distal tubule	Increased gastrointestinal loss	Urine K ⁺ < 20–30 mmol/L
Upper gastrointestinal tract: Vomiting	Nasogastric aspiration	Loss of gastric acid	Associated with metabolic alkalosis	Lower gastrointestinal tract: Diarrhoea	Laxative abuse	Villous adenoma	Bowel obstruction/fistula	Ureterosigmoidostomy
Associated with metabolic acidosis	14.15 Causes of hypokalaemia							

362 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE Investigations Measurement of plasma electrolytes, bicarbonate, urine potassium and sometimes of plasma calcium and magnesium is usually sufficient to establish the diagnosis. If the diagnosis remains unclear, plasma renin should be measured. Levels are low in patients with primary hyperaldosteronism (p. 674) and other forms of mineralocorticoid excess, but raised in other causes of hypokalaemia. When there is no obvious clinical clue to which pathway is involved, measurement of urinary potassium may be helpful; if the kidney is the route of potassium loss, the urine potassium is high (> 30 mmol/24 hrs), whereas if potassium is being lost through the gastrointestinal tract, the kidney retains potassium, resulting in a lower urinary potassium (generally < 20 mmol/24 hrs). It should be noted, however, that if gastrointestinal fluid loss is also associated with hypovolaemia, activation of the

renin-angiotensin-aldosterone system may occur, causing increased loss of potassium in the urine. The cause of hypokalaemia may remain unclear despite the above investigations when urinary potassium measurements are inconclusive and the history is incomplete or unreliable. Many such cases are associated with metabolic alkalosis, and in this setting the measurement of urine chloride concentration can be helpful. A low urine chloride (< 30 mmol/L) is characteristic of vomiting (spontaneous or self-induced, in which chloride is lost in HCl in the vomit), while a urine chloride > 40 mmol/L suggests diuretic therapy (acute phase) or a tubular disorder such as Bartter's or Gitelman's syndrome. Differentiation between occult diuretic use and primary tubular disorders can be achieved by performing a screen of urine for diuretic drugs.

Management
Treatment of hypokalaemia involves first determining the cause and correcting this where possible. If the problem is mainly one of redistribution of potassium into cells, reversal of the process responsible may be sufficient to restore plasma potassium without providing supplements. In most cases, however, some form of potassium replacement will be required. This can generally be achieved with slow-release potassium chloride tablets, but in more acute circumstances intravenous potassium chloride may be necessary. The rate of administration depends on the severity of hypokalaemia and the presence of cardiac or neuromuscular complications, but should generally not exceed 10 mmol of potassium per hour. In patients with severe, life-threatening hypokalaemia, the concentration of potassium in the infused fluid may be increased to 40 mmol/L if a peripheral vein is used, but higher concentrations must be infused into a large 'central' vein with continuous cardiac monitoring. In the less common situation where hypokalaemia occurs in the presence of systemic acidosis, alkaline salts of potassium, such as potassium bicarbonate, can be given by mouth. If magnesium depletion is also present, replacement of magnesium may also be required, since low cell magnesium can promote tubular potassium secretion, causing ongoing urinary losses. In some circumstances, potassium-sparing diuretics, such as amiloride, can assist in the correction of hypokalaemia, hypomagnesaemia and metabolic alkalosis, especially when renal loss of potassium is the underlying cause.

Hyperkalaemia
Hyperkalaemia is a common electrolyte disorder, which is defined as existing when serum K^+ is > 5 mmol/L. The causes of hyperkalaemia are summarised in Box 14.16.

Pathophysiology
It is important to remember that hyperkalaemia can be artefactual due to haemolysis of blood specimens during collection or in vitro, or due to release of potassium from platelets in patients with thrombocytosis. True hyperkalaemia, however, can occur either because of redistribution of potassium between the ICF and ECF, or because potassium intake exceeds excretion.

Redistribution
Cause Other features and comment
Artefactual
Haemolysis during venepuncture Haemolysis in vitro Thrombocytosis/leucocytosis Release of intracellular K^+ during sample collection, transit or clotting
Increased intake Dietary potassium
Potassium-containing intravenous fluids
Redistribution from cells Acidosis Insulin deficiency Severe hyperglycaemia β -adrenergic blockers (β -blockers) Hyperkalaemic periodic paralysis
Rhabdomyolysis Severe haemolysis Tumour lysis syndrome Caused by flux of intracellular K^+ into plasma
Reduced urinary excretion Reduced glomerular filtration: Acute kidney injury Chronic kidney disease Plasma creatinine typically

“ 500 μ mol/L (5.67 mg/dL) Reduced mineralocorticoid receptor activation: Addison's disease Congenital adrenal hyperplasia Isolated aldosterone deficiency Angiotensin-converting enzyme (ACE) inhibitors Angiotensin-receptor blockers (ARBs) ACE inhibitors and ARBs reduce aldosterone levels Calcineurin

inhibitors Spironolactone Eplerenone All block the mineralocorticoid receptor
 Heparin Heparin inhibits aldosterone production Inhibitors of renin production:
 Non-steroidal antiinflammatory drugs (NSAIDs) β -blockers Tubulointerstitial
 disease: Interstitial nephritis Diabetic nephropathy Obstructive uropathy Other:
 Amiloride Blocks K^+ exchange in distal tubule Gordon's syndrome Direct effect
 on K^+ transport in renal tubule } } } } 14.16 Causes of hyperkalaemia

Acid-base homeostasis • 363

serum potassium constitutes severe hyperkalaemia and requires urgent treatment. Patients who have potassium concentrations < 6.5 mmol/L in the absence of neuromuscular symptoms or ECG changes can be treated with a reduction of potassium intake and correction of predisposing factors. However, in acute and/ or severe hyperkalaemia (plasma potassium > 6.5 – 7.0 mmol/L), more urgent measures must be taken (Box 14.17). The first step should be infusion of 10 mL 10% calcium gluconate to stabilise conductive tissue membranes (calcium has the opposite effect to potassium on conduction of an action potential). Measures to shift potassium from the ECF to the ICF should also be applied, as they generally have a rapid effect and may avert arrhythmias. Ultimately, a means of removing potassium from the body is generally necessary. When renal function is reasonably preserved, loop diuretics (accompanied by intravenous saline if hypovolaemia is present) may be effective. In renal failure, dialysis may be required. Oral ion exchange resins, such as sodium polystyrene sulfonate (SPS), have traditionally been used to bind and excrete gastrointestinal potassium. There are concerns, however, with regard to SPS's lack of proven efficacy and safety, with a number of reports of intestinal necrosis associated with its use. Alternative cation exchanges have been developed and are currently being trialled, with the aim of providing more effective and safer alternatives for the treatment of hyperkalaemia.

Acid-base homeostasis The pH of arterial plasma is normally 7.40, corresponding to an H^+ concentration of 40 nmol/L, and under normal circumstances H^+ concentrations do not vary outside the range of 37–45 nmol/L (pH 7.43–7.35). Abnormalities of acid-base balance can occur in a wide range of diseases. Increases in H^+ concentration cause acidosis with a decrease in pH, whereas decreases in H^+ concentration cause alkalosis with a rise in pH.

Functional anatomy and physiology A variety of physiological mechanisms maintain pH of the ECF within narrow limits. The first is the action of blood and tissue buffers, of which the most important involves reaction of H^+ ions with bicarbonate to form carbonic acid, which, under the of potassium from the ICF to the ECF may take place in the presence of systemic acidosis, or when the circulating levels of insulin, catecholamines and aldosterone are reduced, or when the effects of these hormones are blocked (p. 361). High dietary potassium intake may contribute to hyperkalaemia, but is seldom the only explanation unless renal excretion mechanisms are impaired. The mechanism of hyperkalaemia in acute kidney injury and chronic kidney disease is impaired excretion of potassium into the urine as the result of a reduced GFR. In addition, acute kidney injury can be associated with severe hyperkalaemia when there is an increased potassium load, such as in rhabdomyolysis or in sepsis, particularly when acidosis is present. In chronic kidney disease, adaptation to moderately elevated plasma potassium levels commonly occurs. However, acute rises in potassium triggered by excessive dietary intake, hypovolaemia or drugs (see below) may occur and destabilise the situation. Hyperkalaemia can also develop when tubular potassium secretory processes are impaired, even if the GFR is normal.

This can arise in association with low levels of aldosterone, as is found in Addison's disease, hyporeninaemic hypoaldosteronism or inherited disorders such as congenital isolated hypoaldosteronism, in which there is a defect in aldosterone biosynthesis, and pseudohypoaldosteronism type 2 (Gordon's syndrome), caused by mutations in the WNK2 and WNK4 genes, which causes decreased potassium secretion in the renal tubules. Drug-induced causes include ACE inhibitors, angiotensinreceptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs) and β -adrenoceptor antagonists (β -blockers). In another group of conditions, tubular potassium secretion is impaired as the result of aldosterone resistance. This can occur in a variety of diseases in which there is inflammation of the tubulointerstitium, such as systemic lupus erythematosus; following renal transplantation; during treatment with potassiumsparing diuretics; and in a number of inherited disorders of tubular transport. In aldosterone deficiency or aldosterone resistance, hyperkalaemia may be associated with acid retention, giving rise to the pattern of hyperkalaemic distal ('type 4') renal tubular acidosis (p. 364). Clinical features Mild to moderate hyperkalaemia (< 6.5 mmol/L) is usually asymptomatic. More severe hyperkalaemia can present with progressive muscular weakness, but sometimes there are no symptoms until cardiac arrest occurs. The typical ECG changes are shown on page 347. Peaking of the T wave is an early ECG sign, but widening of the QRS complex presages a dangerous cardiac arrhythmia. However, these characteristic ECG findings are not always present, even in severe hyperkalaemia. Investigations Measurement of electrolytes, creatinine and bicarbonate, when combined with clinical assessment, usually provides the explanation for hyperkalaemia. In aldosterone deficiency, plasma sodium concentration is characteristically low, although this can occur with many causes of hyperkalaemia. Addison's disease should be excluded unless there is an obvious alternative diagnosis, as described on page 671. Management Treatment of hyperkalaemia depends on its severity and the rate of development, but opinions vary as to what level of 14.17 Treatment of severe hyperkalaemia Objective Therapy Stabilise cell membrane potential1 IV calcium gluconate (10 mL of 10% solution) Shift K^+ into cells Inhaled β_2 -adrenoceptor agonist IV glucose (50 mL of 50% solution) and insulin (5 IU Actrapid) IV sodium bicarbonate2 Remove K^+ from body IV furosemide and normal saline3 Ion-exchange resin (e.g. Resonium) orally or rectally Dialysis 1If severe hyperkalaemia (K^+ typically > 6.5 mmol/L). 2If acidosis present. 3If adequate residual renal function.

364 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE are generated in the tubular cell from the hydration of CO_2 to form carbonic acid, which dissociates into an H^+ ion secreted lumenally, and a bicarbonate ion that passes across the basolateral membrane into the blood. The secreted H^+ ions contribute to the reabsorption of any residual bicarbonate present in the luminal fluid, by generating intracellular OH^- that reacts with CO_2 to form HCO_3^- , which exits across the basolateral membrane. However, H^+ secretion also contributes net acid for removal from the body, bound to a variety of urinary buffers, of which phosphate and ammonia are the most important. Urinary buffers are required to prevent a reduction in urinary pH, which would create an unfavourable gradient that would prevent further H^+ secretion. Filtered phosphate (HPO_4^{2-}) combines with H^+ in the distal tubular lumen to form dihydrogen phosphate ($H_2PO_4^-$), which is excreted in the urine with sodium. Ammonia (NH_3) is generated within tubular cells by deamination of the amino acid glutamine by the enzyme glutaminase. The NH_3 then reacts with secreted H^+ in the tubular lumen to form ammonium (NH_4^+), which becomes trapped in the luminal fluid and is excreted with chloride ions. These two mechanisms remove approximately 1 mmol/kg of hydrogen ions from the body per day, which equates to the non-volatile acid load arising from the

metabolism of dietary protein. The slightly alkaline plasma pH of 7.4 (H^+ 40 nmol/L) that is maintained during health can be accounted for by the kidney's ability to generate an acidic urine (typically pH 5–6 (H^+ 1000–10 000 nmol/L), in which the net daily excess of metabolic acid produced by the body can be excreted. Presenting problems in acid–base balance Patients with disturbances of acid–base balance may present clinically either with the effects of tissue malfunction due to disturbed pH (such as altered cardiac and central nervous system function), or with secondary changes in respiration that occur as a response to the underlying metabolic change (such as Kussmaul respiration during metabolic acidosis). The clinical picture is often dominated by the underlying cause rather than the acid–base abnormality itself. Frequently, acid–base disturbances only become evident when the venous plasma bicarbonate concentration is measured and found to be abnormal, or when blood gas analysis shows abnormalities in pH, PCO_2 or bicarbonate. The most common patterns of abnormality in blood gas parameters are shown in Box 14.18. Note that the terms acidosis and alkalosis strictly refer to the underlying direction of the acid–base change, while acidaemia and alkalaemia more correctly refer to the net change present in the blood. Interpretation of arterial blood gases is also described on page 555. In metabolic disturbances, respiratory compensation is almost immediate, so that the predicted compensatory change in PCO_2 is achieved soon after the onset of the metabolic disturbance. In respiratory disorders, on the other hand, a small initial change in bicarbonate occurs as a result of chemical buffering of CO_2 , largely within red blood cells, but over days and weeks the kidney achieves further compensatory changes in bicarbonate concentration as a result of long-term adjustments in acid secretory capacity. When the clinically obtained acid–base parameters do not accord with the predicted compensation shown, a mixed acid–base disturbance should be suspected (p. 367). Metabolic acidosis Metabolic acidosis occurs when an acid other than carbonic acid (due to CO_2 retention) accumulates in the body, resulting in a influence of the enzyme carbonic anhydrase (CA), dissociates to form CO_2 and water: $CO_2 + H_2O \rightleftharpoons H^+ + HCO_3^-$ CA

•
 $\leftrightarrow + + - \rightleftharpoons$ This buffer system is important because bicarbonate is present at a relatively high concentration in ECF (21–29 mmol/L), and two of its key components are under physiological control: CO_2 by the lungs, and bicarbonate by the kidneys. These relationships are illustrated in Figure 14.10 (a form of the Henderson–Hasselbalch equation). Respiratory compensation for acid–base disturbances can occur quickly. In response to acid accumulation, pH changes in the brainstem stimulate ventilatory drive, reduce PCO_2 and increase pH (p. 555). Conversely, systemic alkalosis leads to inhibition of ventilation, causing a rise in PCO_2 and reduction in pH, although it should be noted that this mechanism has limited capacity to change pH because hypoxia provides an alternative stimulus to drive ventilation. The kidneys provide a third line of defence against disturbances of arterial pH. When acid accumulates due to chronic respiratory or metabolic (non-renal) causes, the kidneys have the long-term capacity to enhance urinary excretion of acid, effectively increasing the plasma bicarbonate. Renal control of acid–base balance Regulation of acid–base balance occurs at several sites in the kidney. The proximal tubule reabsorbs about 85% of the filtered bicarbonate ions, through the mechanism for H^+ secretion illustrated in Figure 14.3A. This is dependent on the enzyme carbonic anhydrase, both in the cytoplasm of the proximal tubular cells and on the luminal surface of the brush border membranes. The system has a high capacity and is required to rescue filtered bicarbonate, but does not lead to significant acidification of the luminal fluid. Distal nephron segments also have an important role in acid excretion. Hydrogen ions are secreted into the lumen by an H^+ -ATPase in the intercalated cells of the cortical

collecting duct and the outer medullary collecting duct cells. The H^+ ions Fig. 14.10 Relationship between pH, PCO_2 (in mmHg) and plasma bicarbonate concentration (in mmol/L). *Note that changes in HCO_3^- concentration are also part of the renal correction for sustained metabolic acid-base disturbances as long as the kidney itself is not the cause of the primary disturbance.* $pH = 6.1 + \log [HCO_3^-] / 0.03 \times PCO_2$ 1° changes in metabolic disturbances 2° changes after renal compensation 2° changes after respiratory compensation 1° changes in respiratory disturbances

Acid-base homeostasis • 365

due to mutations in the genes that regulate acid or bicarbonate transport in the renal tubules (see Fig. 14.3). Acidosis with an increased anion gap is most commonly seen in ketoacidosis, renal failure and lactic acidosis, where there is endogenous production of anions distinct from Cl^- and HCO_3^- . Ketoacidosis is caused by insulin deficiency and is exacerbated by catecholamine and stress hormone excess, which combine to cause lipolysis and the formation of acidic ketones (acetoacetate, 3-hydroxybutyrate and acetone). The most common cause of ketoacidosis is diabetic ketoacidosis (DKA); its aetiology and management are discussed on page 735. Starvation ketoacidosis occurs when there is reduced food intake in situations of high glucose demand, such as in neonates, and in pregnant or breastfeeding women. In alcoholic ketoacidosis, there is usually a background of chronic malnutrition and a recent alcohol binge. Two subtypes of lactic acidosis have been defined: • type 1, due to tissue hypoxia and peripheral generation of lactate, as in patients with circulatory failure and shock • type 2, due to impaired metabolism of lactate, as in liver disease or by a number of drugs and toxins, including metformin, which inhibit lactate metabolism (p. 746). Metabolic acidosis with an increased anion gap may also be a consequence of exogenous acid loads from poisoning with aspirin, methanol or ethylene glycol. 14.18 Principal patterns of acid-base disturbance

Disturbance	Blood H^+	Primary change	Compensatory response	Predicted compensation
Metabolic acidosis	↓	↓ HCO_3^-	↓ PCO_2	$PCO_2 \text{ fall in kPa} = 0.16 \times HCO_3^- \text{ fall in mmol/L}$
Metabolic alkalosis	↑	↑ HCO_3^-	↑ PCO_2	$PCO_2 \text{ rise in kPa} = 0.08 \times HCO_3^- \text{ rise in mmol/L}$
Respiratory acidosis	↓	↑ PCO_2	↑ HCO_3^-	Acute: $HCO_3^- \text{ rise in mmol/L} = 0.75 \times PCO_2 \text{ rise in kPa}$ Chronic: $HCO_3^- \text{ rise in mmol/L} = 2.62 \times PCO_2 \text{ rise in kPa}$
Respiratory alkalosis	↑	↓ PCO_2	↓ HCO_3^-	Acute: $HCO_3^- \text{ fall in mmol/L} = 1.50 \times PCO_2 \text{ fall in kPa}$ Chronic: $HCO_3^- \text{ fall in mmol/L} = 3.75 \times PCO_2 \text{ fall in kPa}$

1H⁺ of 40 nmol/L = pH of 7.40. 2PCO₂ of 5.33 kPa = 40 mmHg. 3PCO₂ does not rise above 7.33 kPa (55 mmHg) because hypoxia then intervenes to drive respiration. fall in the plasma bicarbonate. The causes of metabolic acidosis are summarised in Box 14.19, subdivided into two categories, depending on whether the anion gap is normal or raised.

401 $HCO_3^- < 24 \text{ mmol/L}$ $PCO_2 < 5.33 \text{ kPa}$ 2 PCO_2 fall in kPa = $0.16 \times HCO_3^-$ fall in mmol/L Metabolic alkalosis < 401 $HCO_3^- > 24 \text{ mmol/L}$ $PCO_2 > 5.33 \text{ kPa}$ 2,3 PCO_2 rise in kPa = $0.08 \times HCO_3^-$ rise in mmol/L Respiratory acidosis 401 $PCO_2 > 5.33 \text{ kPa}$ 2 $HCO_3^- > 24 \text{ mmol/L}$ Acute: HCO_3^- rise in mmol/L = $0.75 \times PCO_2$ rise in kPa Chronic: HCO_3^- rise in mmol/L = $2.62 \times PCO_2$ rise in kPa Respiratory alkalosis < 401 $PCO_2 < 5.33 \text{ kPa}$ 2 $HCO_3^- < 24 \text{ mmol/L}$ Acute: HCO_3^- fall in mmol/L = $1.50 \times PCO_2$ fall in kPa Chronic: HCO_3^- fall in mmol/L = $3.75 \times PCO_2$ fall in kPa 1H⁺ of 40 nmol/L = pH of 7.40. 2PCO₂ of 5.33 kPa = 40 mmHg. 3PCO₂ does not rise above 7.33 kPa (55 mmHg) because hypoxia then intervenes to drive respiration. fall in the plasma bicarbonate. The causes of metabolic acidosis are summarised in Box 14.19, subdivided into two categories, depending on whether the anion gap is normal or raised.

Pathophysiology Metabolic acidosis with a normal anion gap occurs when there is a primary loss of bicarbonate from the ECF, or when there is poisoning with or therapeutic infusion of a mineral acid such as hydrochloric acid or ammonium chloride. Renal tubular acidosis (RTA) is an important cause of metabolic acidosis with a normal anion gap. It can be caused by a defect in one of three

processes: • impaired bicarbonate reabsorption in the proximal tubule (proximal RTA) • impaired acid secretion in the late distal tubule or cortical collecting duct intercalated cells (classical distal RTA) • impaired sodium reabsorption in the late distal tubule or cortical collecting duct, which is associated with reduced secretion of both potassium and H⁺ ions (hyperkalaemic distal RTA). Various subtypes of RTA are recognised and the most common causes are shown in Box 14.20. The inherited forms of RTA are 14.20 Causes of renal tubular acidosis

Proximal renal tubular acidosis (type II RTA) • Inherited: Fanconi's syndrome Cystinosis Wilson's disease • Paraproteinaemia: Myeloma • Amyloidosis • Hyperparathyroidism • Heavy metal toxicity: Lead, cadmium and mercury poisoning • Drugs: Carbonic anhydrase inhibitors Ifosfamide Classical distal renal tubular acidosis (type I RTA) • Inherited • Autoimmune diseases: Systemic lupus erythematosus Sjögren's syndrome • Hyperglobulinaemia • Toxins and drugs: Toluene Lithium Amphotericin Hyperkalaemic distal renal tubular acidosis (type IV RTA) • Hypoaldosteronism (primary or secondary) • Obstructive nephropathy • Renal transplant rejection • Drugs: Amiloride Spironolactone

14.19 Causes of metabolic acidosis Disorder Mechanism Normal anion gap Ingestion or infusion of inorganic acid Therapeutic infusion of or poisoning with NH₄Cl, HCl Gastrointestinal HCO₃⁻ loss Loss of HCO₃⁻ – in diarrhoea, small bowel fistula, urinary diversion procedure Renal tubular acidosis (RTA) Urinary loss of HCO₃⁻ – in proximal RTA; impaired tubular acid secretion in distal RTA Increased anion gap Endogenous acid load Diabetic ketoacidosis Accumulation of ketones¹ with hyperglycaemia (p. 735) Starvation ketosis Alcoholic ketoacidosis Accumulation of ketones without hyperglycaemia (p. 725) Lactic acidosis Shock, liver disease, drugs Kidney disease Accumulation of organic acids Exogenous acid load Aspirin poisoning Accumulation of salicylate² Methanol poisoning Accumulation of formate Ethylene glycol poisoning Accumulation of glycolate, oxalate ¹Ketones include acid anions acetoacetate and β-hydroxybutyrate (p. 725). ²Salicylate poisoning is also associated with respiratory alkalosis due to direct ventilatory stimulation. }

366 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE needed. In alcoholism and starvation ketosis, intravenous glucose is indicated. By stimulating endogenous insulin secretion, this will reverse hepatic ketone production. Malnourished patients may also require thiamin, potassium, magnesium and phosphate supplements (p. 706). Use of intravenous bicarbonate in metabolic acidosis is controversial. Because rapid correction of acidosis can induce hypokalaemia or a fall in plasma ionised calcium, the use of bicarbonate infusions is best reserved for situations where the underlying disorder cannot be readily corrected and acidosis is severe (H⁺ > 100 nmol/L, pH < 7.00) or associated with evidence of tissue dysfunction. The acidosis in RTA can sometimes be controlled by treating the underlying cause (see Box 14.20), but usually supplements of sodium and potassium bicarbonate are also necessary in types I and II RTA to achieve a target plasma bicarbonate level of > 18 mmol/L and normokalaemia. In type IV RTA, loop diuretics, thiazides or fludrocortisone (as appropriate to the underlying diagnosis) may be effective in correcting the acidosis and the hyperkalaemia. Metabolic alkalosis Metabolic alkalosis is characterised by an

increase in the plasma bicarbonate concentration and the plasma pH (see Box 14.18). There is a compensatory rise in PCO₂ due to hypoventilation but this is limited by the need to avoid hypoxia. Classical causes include primary hyperaldosteronism (Conn's syndrome, p. 674), Cushing's syndrome (p. 666) and glucocorticoid therapy (p. 670). Occasionally, overuse of antacid salts for treatment of dyspepsia produces a similar pattern. Pathophysiology Metabolic alkalosis is best classified according to the accompanying changes in ECF volume. Hypovolaemic metabolic alkalosis is the most common pattern. This can be caused by sustained vomiting, in which acid-rich fluid is lost directly from the body, or by treatment with loop diuretics or thiazides. In the case of sustained vomiting, loss of gastric acid is the immediate cause of the alkalosis, but several factors act to sustain or amplify this in the context of volume depletion (Fig. 14.11). Loss of sodium and fluid leads to hypovolaemia and secondary hyperaldosteronism, triggering proximal sodium bicarbonate reabsorption and additional acid secretion by the distal tubule. Hypokalaemia occurs due to potassium loss in the vomitus and by the kidney as the result of secondary hyperaldosteronism, and itself is a stimulus to acid secretion. Additionally, the compensatory rise in PCO₂ further enhances tubular acid secretion. The net result is sustained metabolic alkalosis with an inappropriately acid urine, which cannot be corrected until the deficit in circulating volume has been replaced. Normovolaemic (or hypervolaemic) metabolic alkalosis occurs when bicarbonate retention and volume expansion occur simultaneously. Clinical features Clinically, apart from manifestations of the underlying cause, there may be few symptoms or signs related to alkalosis itself. When the rise in systemic pH is abrupt, however, plasma ionised calcium falls and signs of increased neuromuscular irritability, such as tetany, may develop (p. 663). Investigations The diagnosis can be confirmed by measurement of electrolytes and arterial blood gases. Clinical features Normal anion gap metabolic acidosis is usually due either to bicarbonate loss in diarrhoea, where the clinical diagnosis is generally obvious, or to RTA. Although some forms of RTA are inherited, it may also be an acquired disorder, and in these circumstances the discovery of metabolic acidosis may serve as an early clue to the underlying diagnosis. The presentation of increased anion gap acidosis is usually dominated by clinical features of the underlying disease, such as uncontrolled diabetes mellitus, kidney failure or shock, or may be suggested by the clinical history of starvation, alcoholism or associated symptoms, such as visual complaints in methanol poisoning (p. 147). Investigations The different types of metabolic acidosis can be distinguished by blood gas measurements, along with measurements of creatinine, electrolytes and bicarbonate. Under normal circumstances, the anion gap, defined as the numerical difference between the main measured cations (Na⁺ + K⁺) and the anions (Cl⁻ + HCO₃⁻) is about 5–11 mmol/L. This gap is normally made up of anions, such as phosphate and sulphate, as well as albumin. RTA should be suspected when there is a hyperchloraemic acidosis with a normal anion gap in the absence of gastrointestinal disturbance. The diagnosis can be confirmed by finding an inappropriately high urine pH (> 5.5) in the presence of systemic acidosis. Sometimes, distal RTA may be incomplete, such that the plasma bicarbonate concentration may be normal under resting conditions. In this case, an acid challenge test can be performed by administration of an acid load in the form of ammonium chloride to reduce plasma bicarbonate. The diagnosis of incomplete distal RTA can be confirmed if the urine pH fails to fall below 5.3 in the presence of a low bicarbonate. The different subtypes of RTA can be differentiated by various biochemical features. Patients with proximal and distal RTA often present with features of profound hypokalaemia, while type IV RTA is associated with hyperkalaemia. Proximal RTA is frequently associated with urinary wasting of amino acids, phosphate and glucose (Fanconi's syndrome), as well as bicarbonate and potassium. Patients with this disorder can lower the urine pH when the acidosis is severe and plasma bicarbonate levels

have fallen below 16 mmol/L, since distal H⁺ secretion mechanisms are intact. In the classical form of distal RTA, however, acid accumulation is relentless and progressive, resulting in mobilisation of calcium from bone and osteomalacia with hypercalciuria, renal stone formation and nephrocalcinosis. Potassium is also lost in classical distal RTA, while it is retained in hyperkalaemic distal RTA. Investigations in patients with raised anion gap metabolic acidosis show features of the underlying cause, such as reduced GFR in renal failure and raised urine or blood ketones in ketoacidosis. In DKA, blood glucose is raised, while in starvation and alcoholic acidosis blood glucose is not elevated and may be low. Measurement of plasma lactate is helpful in the diagnosis of lactic acidosis when values are increased over the normal maximal level of 2 mmol/L.

Management The first step in management of metabolic acidosis is to identify and correct the underlying cause when possible (see Box 14.19). This may involve controlling diarrhoea, treating diabetes mellitus, correcting shock, stopping drugs that might cause the condition, or using dialysis to remove toxins. Since metabolic acidosis is frequently associated with sodium and water depletion, resuscitation with intravenous fluids is often

Magnesium homeostasis • 367

in plasma pH. If the condition is sustained, renal compensation occurs, such that tubular acid secretion is reduced and the plasma bicarbonate falls. Respiratory alkalosis is usually of short duration, occurring in anxiety states or as the result of over-vigorous assisted ventilation. It can be prolonged in the context of pregnancy, pulmonary embolism, chronic liver disease, and ingestion of certain drugs such as salicylates that directly stimulate the respiratory centre in the brainstem. Clinical features are those of the underlying cause but agitation associated with perioral and digital tingling may also occur, as alkalosis promotes the binding of calcium to albumin, resulting in a reduction in ionised calcium concentrations. In severe cases, Trousseau's sign and Chvostek's sign may be positive, and tetany or seizures may develop (p. 663). Management involves correction of identifiable causes, reduction of anxiety, and a period of rebreathing into a closed bag to allow CO₂ levels to rise.

Mixed acid-base disorders It is not uncommon for more than one disturbance of acid-base metabolism to be present at the same time in the same patient: for example, a respiratory acidosis due to narcotic overdose with metabolic alkalosis due to vomiting. In these situations, the arterial pH will represent the net effect of all primary and compensatory changes. Indeed, the pH may be normal, but the presence of underlying acid-base disturbances can be gauged from concomitant abnormalities in the PCO₂ and bicarbonate concentration. In assessing these disorders, all clinical influences on the patient's acid-base status should be identified, and reference should be made to the table of predicted compensation given in Box 14.18. If the compensatory change is discrepant from the rules of thumb provided, more than one disturbance of acid-base metabolism may be suspected.

Calcium homeostasis Disorders of calcium homeostasis are discussed in Chapter 18 and bone disease is discussed in Chapter 24.

Magnesium homeostasis Magnesium is mainly an intracellular cation. It is important to the function of many enzymes, including the Na,K-ATPase, and can regulate both potassium and calcium channels. Its overall effect is to stabilise excitable cell membranes.

Functional anatomy and physiology Renal handling of magnesium involves filtration of free plasma magnesium at the glomerulus (about 70% of the total), with extensive reabsorption (50–70%) in the loop of Henle and other parts of the proximal and distal renal tubule. Magnesium reabsorption is also enhanced by parathyroid hormone (PTH).

Presenting problems in magnesium homeostasis Disturbances in magnesium homeostasis usually occur because of increased loss of magnesium through the gut or kidney or

Management Metabolic alkalosis with hypovolaemia can be corrected by intravenous infusions of 0.9% saline with potassium supplements. This reverses the secondary hyperaldosteronism and allows the kidney to excrete the excess alkali in the urine. In metabolic alkalosis with normal or increased volume, treatment should focus on management of the underlying endocrine cause (Ch. 18).

Respiratory acidosis Respiratory acidosis occurs when there is accumulation of CO₂ due to type II respiratory failure (p. 565). This results in a rise in the PCO₂, with a compensatory increase in plasma bicarbonate concentration, particularly when the disorder is of long duration and the kidney has fully developed its capacity for increased acid excretion. This acid-base disturbance can arise from lesions anywhere along the neuromuscular pathways from the brain to the respiratory muscles that result in impaired ventilation. It can also arise during intrinsic lung disease if there is significant mismatching of ventilation and perfusion. Clinical features are primarily those of the underlying cause of the respiratory disorder, such as paralysis, chest wall injury or chronic obstructive lung disease, but the CO₂ accumulation may itself lead to drowsiness that further depresses respiratory drive. Management involves correction of causative factors where possible, but ultimately ventilatory support may be necessary.

Respiratory alkalosis Respiratory alkalosis develops when there is a period of sustained hyperventilation, resulting in a reduction of PCO₂ and increase Fig. 14.11 Generation and maintenance of metabolic alkalosis during prolonged vomiting. Loss of H⁺Cl⁻ generates metabolic alkalosis, which is maintained by renal changes. Vomiting Na⁺Cl⁻ Metabolic alkalosis Gastric loss of H⁺Cl⁻ K⁺Cl⁻ Hypovolaemia ↑ Proximal Na⁺HCO₃⁻ reabsorption ↑ Renin - angiotensin - aldosterone Hypokalaemia ↑ Distal H⁺ secretion ↑ Renal NH₃ synthesis ↑ H⁺ excretion

368 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE Management The underlying cause should be identified and treated where possible. When symptoms are present, the treatment of choice is intravenous magnesium chloride at a rate not exceeding 0.5 mmol/kg in the first 24 hours. If intravenous access is not feasible, magnesium sulphate can be given intramuscularly. Oral magnesium salts have limited effectiveness due to poor absorption and may cause diarrhoea. If hypomagnesaemia is caused by diuretic treatment, adjunctive use of a potassium-sparing agent can also help by reducing magnesium loss into the urine. Hypermagnesaemia This is a much less common abnormality than hypomagnesaemia. Predisposing conditions include acute kidney injury, chronic kidney disease and adrenocortical insufficiency. The condition is generally precipitated in patients at risk from an increased intake of magnesium, or from the use of magnesium-containing medications, such as antacids, laxatives and enemas. Clinical features include bradycardia, hypotension, reduced consciousness and respiratory depression. Management involves ceasing all magnesium-containing drugs and reducing dietary magnesium intake, improving renal function if possible, and promoting urinary magnesium excretion using a loop diuretic with intravenous hydration, if residual renal function allows. Calcium gluconate may be given intravenously to ameliorate cardiac effects. Dialysis may be necessary in patients with poor renal function.

Phosphate homeostasis Inorganic phosphate (mainly present as HPO₄²⁻) is intimately involved in cell energy metabolism, intracellular signalling and bone and mineral homeostasis (Ch. 24). The normal plasma concentration is 0.8–1.4 mmol/L (2.48–4.34 mg/dL). Functional anatomy and physiology Phosphate is freely filtered at the glomerulus and approximately 65% is reabsorbed by the proximal tubule, through an apical sodium-phosphate co-transport carrier. A further 10–20% is reabsorbed in the distal tubules, leaving a fractional excretion of some 10% to pass into the urine, usually as H₂PO₄⁻. Proximal reabsorption is decreased by PTH, fibroblast growth factor 23 (FGF23), volume expansion, osmotic diuretics and glucose infusion. Presenting problems in

phosphate homeostasis The following section deals primarily with conditions that cause acute disturbances in serum phosphate concentrations. Chronic disorders that are accompanied by phosphate depletion, such as osteomalacia and hypophosphataemic rickets, are discussed in Chapter 24. Acute kidney injury and chronic kidney disease, which are associated with hyperphosphataemia, are discussed below and also in Chapter 15.

Hypophosphataemia Hypophosphataemia is defined as existing when serum phosphate values fall below 0.8 mmol/L (2.48 mg/dL). The causes are shown in Box 14.22, subdivided into the underlying pathogenic mechanisms.

inability to excrete magnesium normally in patients with renal impairment.

Hypomagnesaemia Hypomagnesaemia is defined as existing when plasma magnesium concentrations are below the reference range of 0.75–1.0 mmol/L (1.5–2.0 mEq/L).

Pathophysiology Hypomagnesaemia usually is a reflection of magnesium depletion (Box 14.21), which can be caused by excessive magnesium loss from the gastrointestinal tract (notably in chronic diarrhoea) or the kidney (during prolonged use of loop diuretics). Excessive alcohol ingestion can cause magnesium depletion through both gut and renal losses. Some inherited tubular transport disorders, such as Gitelman's and Bartter's syndromes, can also result in urinary magnesium wasting (p. 361). Magnesium depletion has important effects on calcium homeostasis because magnesium is required for the normal secretion of PTH in response to a fall in serum calcium, and because hypomagnesaemia causes end-organ resistance to PTH.

Clinical features Mild degrees of hypomagnesaemia may be asymptomatic but more severe hypomagnesaemia may be associated with symptoms of hypocalcaemia, such as tetany, cardiac arrhythmias (notably torsades de pointes, p. 476), central nervous excitation and seizures, vasoconstriction and hypertension. Hypomagnesaemia and magnesium depletion are also associated (through uncertain mechanisms) with hyponatraemia and hypokalaemia, which may contribute to some of the clinical manifestations.

14.21 Causes of hypomagnesaemia

Mechanism

Examples

Inadequate intake
 Starvation
 Malnutrition
 Alcoholism
 Parenteral alimentation

Excessive losses
 Gastrointestinal
 Prolonged vomiting/nasogastric aspiration
 Chronic diarrhoea/laxative abuse
 Malabsorption
 Small bowel bypass surgery
 Fistulae

Urinary
 Diuretic therapy
 Alcohol
 Tubulotoxic drugs: Gentamicin
 Cisplatin

Volume expansion
 Diabetic ketoacidosis
 Post-obstructive diuresis
 Recovery from acute tubular necrosis

Inherited tubular transport defect: Bartter's syndrome
 Gitelman's syndrome

Primary renal magnesium wasting
 Miscellaneous
 Acute pancreatitis
 Foscarnet therapy
 Proton pump inhibitor therapy
 Hungry bone syndrome
 Diabetes mellitus

Disorders of amino acid metabolism • 369

primary hyperparathyroidism and hypophosphataemic rickets are described in more detail on pages 664 and 1053.

Hyperphosphataemia Hyperphosphataemia is most commonly caused by acute kidney injury or chronic kidney disease (pp. 413 and 419).

Pathophysiology In acute kidney injury and chronic kidney disease, the primary cause is reduced phosphate excretion as the result of a low GFR. In contrast, the hyperphosphataemia in hypoparathyroidism and pseudohypoparathyroidism is due to increased tubular phosphate reabsorption. Redistribution of phosphate from cells into the plasma can also be a contributing factor in the tumour lysis syndromes and other catabolic states. Phosphate accumulation can be aggravated in any of these conditions if the patient takes phosphate-containing preparations or inappropriate vitamin D therapy.

Clinical features The clinical features relate to hypocalcaemia and metastatic calcification, particularly in chronic kidney disease with tertiary hyperparathyroidism (when a high calcium–phosphate product occurs).

Management Hyperphosphataemia in patients with kidney

disease should be treated with dietary phosphate restriction and the use of oral phosphate binders (p. 418). Hyperphosphataemia in hypoparathyroidism and pseudohypoparathyroidism does not usually require treatment. Hyperphosphataemia associated with tumour lysis syndromes and catabolic states can be treated with intravenous normal saline, which is given to promote phosphate excretion.

Disorders of amino acid metabolism

Congenital disorders of amino acid metabolism usually present in the neonatal period and may involve life-long treatment regimens. However, some disorders, particularly those involved in amino acid transport, may not present until later in life.

Phenylketonuria Phenylketonuria (PKU) is inherited as an autosomal recessive disorder caused by loss-of-function mutations in the PAH gene, which encodes phenylalanine hydroxylase, an enzyme required for degradation of phenylalanine. As a result, phenylalanine accumulates at high levels in the neonate's blood, causing intellectual disability. The diagnosis of PKU is almost always made by routine neonatal screening (p. 56). Treatment involves life-long adherence to a low-phenylalanine diet. Early and adequate dietary treatment prevents major intellectual disability, although there may still be a slight reduction in IQ.

Homocystinuria Homocystinuria is an autosomal recessive disorder caused by loss-of-function mutations in the CBS gene, which encodes cystathionine β -synthase. The enzyme deficiency causes accumulation of homocysteine and methionine in the blood. Many cases of homocystinuria are diagnosed through newborn screening programmes.

Pathophysiology Phosphate may redistribute into cells during periods of increased energy utilisation (such as refeeding after a period of starvation) and during systemic alkalosis. However, severe hypophosphataemia usually represents an overall body deficit due to either inadequate intake or absorption through the gut, or excessive renal losses, most notably in primary hyperparathyroidism (p. 663) or as the result of acute plasma volume expansion, osmotic diuresis and diuretics acting on the proximal renal tubule. Less common causes include inherited defects of proximal sodium-phosphate co-transport and tumour-induced osteomalacia due to ectopic production of the hormone FGF23 (p. 1053).

Clinical features The clinical features of phosphate depletion are wide-ranging, reflecting the involvement of phosphate in many aspects of metabolism. Defects appear in the blood (impaired function and survival of all cell lineages), skeletal muscle (weakness, respiratory failure), cardiac muscle (congestive cardiac failure), smooth muscle (ileus), central nervous system (decreased consciousness, seizures and coma) and bone (osteomalacia in severe prolonged hypophosphataemia, p. 1053).

Investigations Measurement of creatinine, electrolytes, phosphate, albumin, calcium and alkaline phosphatase should be performed. In selected cases, measurement of PTH and 25(OH)D may be helpful to exclude osteomalacia or hypophosphataemic rickets. The combination of hypophosphataemia and hypercalcaemia suggests primary hyperparathyroidism, which should be further investigated by measurements of PTH, as described on page 663. The presence of hypocalcaemia suggests hypophosphataemic rickets, which should be further investigated as described on page 1053.

Management Management of hypophosphataemia due to decreased dietary intake or excessive losses involves administering oral phosphate supplements and high-protein/high-dairy dietary supplements that are rich in naturally occurring phosphate. Intravenous treatment with sodium or potassium phosphate salts can be used in critical situations, but there is a risk of precipitating hypocalcaemia and metastatic calcification.

14.22 Causes of hypophosphataemia

Mechanism Examples

- Redistribution into cells
- Refeeding after starvation
- Respiratory alkalosis
- Treatment for diabetic ketoacidosis
- Inadequate intake or absorption
- Malnutrition
- Malabsorption
- Chronic diarrhoea
- Phosphate binders
- Antacids
- Vitamin D deficiency or resistance
- Increased renal excretion
- Hyperparathyroidism
- Extracellular fluid volume expansion with diuresis
- Osmotic diuretics
- Fanconi's syndrome
- Familial hypophosphataemic rickets
- Tumour-induced hypophosphataemic

370 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE after the physician who first described the condition (Box 14.23). Most forms of GSD are inherited in an autosomal recessive manner. The diagnosis of GSD is made on the basis of the symptoms, physical examination and results of biochemical tests. Occasionally, a muscle or liver biopsy is required to confirm the enzyme defect. Different types of GSD present at different ages, and some may require life-long modifications of diet and lifestyle.

Disorders of complex lipid metabolism Complex lipids are key components of the cell membrane that are normally catabolised in organelles called lysosomes. The lysosomal storage diseases are a heterogeneous group of disorders caused by loss-of-function mutations in various lysosomal enzymes (Box 14.24), resulting in an inability to break down complex glycolipids or other intracellular macromolecules. These disorders have diverse clinical manifestations, typically including intellectual disability. Some can be treated with enzyme replacement therapy, while others (such as Tay-Sachs disease) can be prevented through community participation in genetic carrier screening programmes.

Lipids and lipoprotein metabolism The three main biological classes of lipid are:

- cholesterol, which is composed of hydrocarbon rings
- triglycerides (TGs), which are esters composed of glycerol linked to three long-chain fatty acids
- phospholipids, which are composed of a hydrophobic 'tail' consisting of two long-chain fatty acids linked through glycerol to a hydrophilic head containing a phosphate group.

Phospholipids are present in cell membranes and are important signalling molecules. Despite their poor water solubility, lipids need to be absorbed from the gastrointestinal tract and transported throughout the body. This is achieved by incorporating lipids within lipoproteins. Plasma cholesterol and TGs are clinically important because they are major treatable risk factors for cardiovascular disease, while severe hypertriglyceridaemia also predisposes to acute pancreatitis. Clinical manifestations are wide-ranging and involve the eyes (ectopia lentis – displacement of the lens), central nervous system (intellectual disability, delayed developmental milestones, seizures, psychiatric disturbances), skeleton (resembling Marfan's syndrome, and also with generalised osteoporosis), vascular system (thrombotic lesions of arteries and veins) and skin (hypopigmentation). Treatment is dietary, involving a methionine-restricted, cystine-supplemented diet, as well as large doses of pyridoxine.

Disorders of carbohydrate metabolism The most common disorder of carbohydrate metabolism is diabetes mellitus, which is discussed in Chapter 20. There are also some rare inherited defects, discussed below.

Galactosaemia Galactosaemia is caused by loss-of-function mutations in the GALT gene, which encodes galactose-1-phosphate uridylyl transferase. It is usually inherited in an autosomal recessive manner. The neonate is unable to metabolise galactose, one of the hexose sugars contained in lactose. Vomiting or diarrhoea usually begins within a few days of ingestion of milk, and the neonate may become jaundiced. Failure to thrive is the most common clinical presentation. The classic form of the disease results in hepatomegaly, cataracts and intellectual disability. Fulminant infection with *Escherichia coli* is a frequent complication. Treatment involves life-long avoidance of galactose- and lactose-containing foods. The widespread inclusion of galactosaemia in newborn screening programmes has resulted in the identification of a number of milder ('Duarte') variants.

Glycogen storage diseases Glycogen storage diseases (GSDs, or glycogenoses) result from inherited defects in one of the many enzymes responsible for the formation or breakdown of glycogen, a complex carbohydrate that can be broken down quickly to release glucose during exercise or between meals. There are several major types of GSD, which are classified by a number, by the name of the defective enzyme, or eponymously.

Type	Eponym	Enzyme deficiency	Clinical features and complications
I	Von Gierke	Glucose-6-phosphatase	Severe hypoglycaemia, lactic acidosis, hepatomegaly, renal disease, osteoporosis, xanthomas

phosphatase Childhood presentation, hypoglycaemia, hepatomegaly II Pompe α -glucosidase (acid maltase) Classical presentation in infancy, muscle weakness (may be severe) III Cori Glycogen debrancher enzyme Childhood presentation, hepatomegaly, mild hypoglycaemia IV Andersen Brancher enzyme Presentation in infancy, severe muscle weakness (may affect heart), cirrhosis V McArdle Muscle glycogen phosphorylase Exercise-induced fatigue and myalgia VI Hers Liver phosphorylase Mild hepatomegaly VII Tarui Muscle phosphofructokinase Exercise-induced fatigue and myalgia IX1 Liver phosphorylase kinase Mild hepatomegaly

Hepatic glycogen synthase Fasting hypoglycaemia, post-prandial hyperglycaemia X2 Muscle phosphoglycerate mutase Exercise-induced myoglobinuria 1Note that type VIII has been merged into type IX and no longer exists as a separate entity. 2Recent progress in molecular genetics has recognised a number of additional, rarer types of glycogen storage disease. These are not shown in this table, which stops at type X.

Lipids and lipoprotein metabolism • 371

Lysosomal storage disease Enzyme deficiency Clinical features Human enzyme replacement therapy Fabry's disease α -galactosidase A Variable age of onset Neurological (pain in extremities) Dermatological (hypohidrosis, angiokeratomas) Cerebrovascular (renal, cardiac, central nervous system) Available for clinical use Gaucher's disease (various types) Glucocerebrosidase Splenic and liver enlargement, with variable severity of disease Some types also have neurological involvement Available for clinical use in some types Mucopolysaccharidosis Hurler's syndrome Hunter's syndrome Sanfilippo's syndrome Morquio's syndrome + several other types Several enzymes involved in breakdown of glycosaminoglycans Vary with syndrome: can cause intellectual disability, skeletal and joint abnormalities, abnormal facies, obstructive respiratory diseases and recurrent respiratory infections Available for clinical use in some types; clinical trials under way for other types Niemann-Pick disease Acid sphingomyelinase Most common presentation is as a progressive neurological disorder, accompanied by organomegaly Some variants do not have neurological symptoms Clinical trials planned for some types GM2-gangliosidosis Tay-Sachs disease Hexosaminidase A Severe progressive neurological disorder Cherry-red spot in macula Organomegaly in Sandhoff's disease Hexosaminidase activator deficiency Hexosaminidase activator Sandhoff's disease Hexosaminidase A and B } Functional anatomy and physiology Lipids are transported and metabolised by apolipoproteins, which combine with lipids to form spherical or disc-shaped lipoproteins, consisting of a hydrophobic core and a less hydrophobic coat (Fig. 14.12). The structure of some apolipoproteins also enables them to act as enzyme co-factors or cell receptor ligands. Variations in lipid and apolipoprotein composition result in distinct classes of lipoprotein that perform specific metabolic functions. Processing of dietary lipid The intestinal absorption of dietary lipid is described on page 768 (see also Fig. 14.13). Enterocytes lining the gut extract monoglyceride and free fatty acids from micelles and re-esterify them into TGs, which are combined with a truncated form of apolipoprotein B (Apo B48) as it is synthesised. Intestinal cholesterol derived from dietary and biliary sources is also absorbed through a specific intestinal membrane transporter termed NPC1L1. This produces chylomicrons containing TG and cholesterol ester that are secreted basolaterally into lymphatic lacteals and carried to the circulation through the thoracic duct. On entering the blood stream, nascent chylomicrons are modified by further addition of apolipoproteins. Chylomicron TGs are hydrolysed by lipoprotein lipase located on the endothelium of tissue capillary beds. This releases fatty acids that are used locally for energy

production or stored as TG in muscle or fat. The residual 'remnant' chylomicron particle is avidly cleared by low-density lipoprotein receptors (LDLRs) in the liver, which recognise Apo E on the remnant lipoproteins. Complete absorption of dietary lipids takes about 6–10 hours, so chylomicrons are usually undetectable in the plasma after a 12-hour fast. The main dietary determinants of plasma cholesterol concentrations are the intake of saturated and trans-unsaturated fatty acids, which reduce LDLR levels (see below), whereas dietary cholesterol has surprisingly little effect on fasting cholesterol levels. Plant sterols and drugs that inhibit cholesterol absorption are effective because they also reduce the re-utilisation of biliary cholesterol. The dietary determinants of plasma TG concentrations are complex since excessive intake of carbohydrate, fat or alcohol may all contribute to increased plasma TG by different mechanisms.

Endogenous lipid synthesis In the fasting state, the liver is the major source of plasma lipids (Fig. 14.13). The liver may acquire lipids by uptake, synthesis or conversion from other macronutrients. These lipids are transported to other tissues by secretion of very low-density lipoproteins (VLDLs), which are rich in TG but differ from chylomicrons in that they are less massive and contain full-length Apo B100. Following secretion into the circulation, VLDLs undergo metabolic processing similar to that of chylomicrons. Hydrolysis of VLDL TG releases fatty acids to tissues and converts VLDLs into 'remnant' particles, referred to as intermediate-density lipoproteins (IDLs). Most IDLs are rapidly cleared by LDLRs in the liver but some are Fig. 14.12 Structure of lipoproteins.

Apolipoprotein Free cholesterol Phospholipid Triglyceride Cholesteryl ester

14.24 Lysosomal storage diseases

372 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE of the half-life of LDLR through PCSK9, and modulation of cholesterol esterification. Cholesterol transport Peripheral tissues are further guarded against excessive cholesterol accumulation by high-density lipoproteins (HDLs; Fig. 14.13). Lipid-poor Apo A1 (derived from the liver, intestine and the outer layer of chylomicrons and VLDL) accepts cellular cholesterol and phospholipid from a specific membrane transporter known as the ATP-binding cassette A1 (ABCA1). This produces small HDLs that are able to accept more free cholesterol from cholesterol-rich regions of the cell membrane known as 'rafts' via another membrane transporter (ABCG1). The cholesterol that has been accepted by these small HDLs is esterified by lecithin cholesterol acyl transferase (LCAT), thus maintaining an uptake gradient and Fig. 14.13 Absorption, transport and storage of lipids. Pathways of lipid transport are shown; in addition, cholesterol ester transfer protein exchanges triglyceride and cholesterol ester between very low-density lipoprotein/chylomicrons and high-/low-density lipoprotein, and free fatty acids released from peripheral lipolysis can be taken up in the liver. (ABCA1/ABCG1 = adenosine triphosphate-binding cassette A1/G1; Apo = apolipoprotein; BA = bile acids; C = cholesterol; CE = cholesterol ester; FFA = free fatty acids; HDL = mature high-density lipoprotein; HL = hepatic lipase; HMGCoAR = hydroxy-methylglutaryl-co-enzyme A reductase; IDL = intermediate-density lipoprotein; iHDL = immature high-density lipoprotein; LCAT = lecithin cholesterol acyl transferase; LDL = low-density lipoprotein; LDLR = low-density lipoprotein receptor (Apo B100 receptor); LPL = lipoprotein lipase; PCSK9 = proprotein convertase subtilisin kexin 9; SRB1 = scavenger receptor B1; TG = triglyceride; VLDL = very low-density lipoprotein) Synthesis Oxidation FFA TG Bile acids (BA) Apo B100 Cholesterol HMGCoAR Synthesis Liver LDLR LDLR HL SRB1 FFA LPL LPL LDLR LDLR degraded ABCA1 ABCG1 Lipid rafts Cholesterol Oxidation Peripheral tissues TG LCAT HDL iHDL Lipid-poor Apo A1 C CE TG CE PCSK9 LDLR degraded LDLR degraded CE TG TG TG CE iHDL IDL TG CE Chylomicron remnant iHDL iHDL TG TG TG CE Chylomicron VLDL LDL Dietary TG, C and CE Biliary BA and C excretion BA reabsorption Post-prandial Endogenous TG supply Endogenous

cholesterol supply Reverse cholesterol transport Biliary excretion/enterohepatic circulation Lymph
TG TG TG CE Chylomicron Small intestine iHDL PCSK9 PCSK9 processed by hepatic lipase, which
converts the particle to an LDL by removing TG and most materials other than Apo B100, and free
and esterified cholesterol. The catabolism of TG-rich chylomicrons and VLDL by lipoprotein lipase is
modulated by Apos C2 and C3 on the surface of these particles. The LDL particles act as a source
of cholesterol for cells and tissues (Fig. 14.13). LDL cholesterol is internalised by receptor-mediated
endocytosis through the LDLR. Delivery of cholesterol via this pathway down-regulates expression
of LDLR and reduces the synthesis and activity of the rate-limiting enzyme for cholesterol
synthesis, hydroxy-methyl-glutaryl-co-enzyme A (HMGCoA) reductase. Another important regulator
of LDLR levels is the sterol-sensitive protease proprotein convertase subtilisin kexin 9 (PCSK9),
which degrades the LDLR. Intracellular free cholesterol concentrations are maintained within a
narrow range by the inhibitory effects of LDL on expression of LRLR, fine-tuning

Lipids and lipoprotein metabolism • 373

than LDL-C, particularly
when TG levels are
increased. The use of non-
fasting samples is increasing
because non-fasting TG is a
more sensitive marker of the
risk of cardiovascular
disease. Nevertheless, a 12-
hour fast is required for

formal diagnosis of the presence of hypertriglyceridaemia or use of the Friedewald equation. Consideration must be given to confounding factors, such as recent illness, after which cholesterol, LDL and HDL levels temporarily decrease in proportion to severity. Results that will affect major decisions, such as initiation of drug therapy, should be

confirmed with a repeat measurement. Elevated levels of TG are common in obesity, diabetes and insulin resistance (Chs 19 and 20), and are frequently associated with low HDL and increased 'small, dense' LDL. Under these circumstances, LDL-C may under-estimate risk. This is one situation in which measurement of non-HDLC

or Apo B may provide more accurate risk assessment.

Presenting problems in lipid metabolism
Hyperlipidaemia can occur in association with various diseases and drugs, as summarised in Box 14.25.

Overt or subclinical hypothyroidism (p. 639) may cause

hypercholesterolaemia, and so measurement of thyroid function is warranted in

most cases, even in the absence of typical symptoms and signs. Once secondary causes are excluded, primary lipid abnormalities may be diagnosed. Primary lipid abnormalities can be classified according to the predominant lipid problem: hypercholesterolaemia, hypertriglyceridaemia or mixed hyperlipidaemia (Box 14.26). Although single-gene

disorders are encountered in all three categories, most cases are due to multiple-gene (polygenic) loci interacting with environmental factors.

Clinical consequences of dyslipidaemia vary somewhat between these causes (pp. 346–347).

Hypercholesterolaemia

Hypercholesterolaemia is a polygenic disorder that is

the most common cause of a mild to moderate increase in remodelling the particle into a mature spherical HDL.

These HDLs release their cholesterol to the liver and other cholesterol-requiring tissues via the scavenger receptor B1 (SRB1). The cholesterol ester transfer protein (CETP) in plasma allows transfer of cholesterol from HDLs or LDLs to VLDLs

or chylomicrons in exchange for TG. When TG is elevated, the action of CETP may reduce HDL cholesterol and remodel LDLs into 'small, dense' LDL particles that may be more atherogenic in the blood-vessel wall. Animal species that lack CETP are resistant to atherosclerosis. Lipids and cardiovascular disease Plasma lipoprotein levels are major modifiable

risk factors for cardiovascular disease. Increased levels of atherogenic lipoproteins (especially LDL, but also IDL, and possibly chylomicron remnants) contribute to the development of atherosclerosis (p. 484). A sub-population of LDL particles bears an additional protein known as apolipoprotein (a), which

shares homology with plasminogen. The combination of LDL and apolipoprotein (a) is known as lipoprotein (a) (Lp(a)). It transports oxidised phospholipid and is regarded as atherogenic because its plasma concentration is an independent risk factor for cardiovascular disease. Following chemical modifications such as

oxidation, Apo B-containing lipoproteins are no longer cleared by normal mechanisms. They trigger a self-perpetuating inflammatory response, during which they are taken up by macrophages to form foam cells, a hallmark of atherosclerotic lesions. These processes also have an adverse effect on endothelial function.

Conversely, HDL removes cholesterol from the tissues to the liver, where it is metabolised and excreted in bile. HDL may also counteract some components of the inflammatory response, such as the expression of vascular adhesion molecules by the endothelium. Consequently, low HDL cholesterol levels, which are often associated

with TG elevation, are also associated with atherosclerosis.

Investigations Lipid measurements are usually performed for the following reasons:

- screening for primary or secondary prevention of cardiovascular disease
- investigation of patients with clinical features of lipid disorders (p. 347) and their relatives
-

monitoring of response to diet, weight control and medication. Abnormalities of lipid metabolism most commonly come to light following these tests. Non-fasting measurements of total cholesterol (TC) and HDL cholesterol (HDL-C) allow estimation of non-HDL cholesterol (non-HDLC, calculated as $TC - HDL-C$), but a 12-hour fasting sample

is required to standardise TG measurement and allow calculation of LDL cholesterol (LDL-C) according to the Friedewald formula:

$$\text{LDL-C} = \text{TC} - \text{HDL-C} - \frac{\text{TG}}{2.2} \text{ mmol/L}$$

$$\text{LDL-C} = \text{TC} - \text{HDL-C} - \frac{\text{TG}}{5} \text{ mg/dL}$$

– –()

The formula becomes unreliable when TG levels exceed 4 mmol/L (350 mg/dL). Measurements of non-HDL-C or Apo B100 may assess risk of cardiovascular disease more accurately.

14.25 Causes of secondary hyperlipidaemia

Secondary hypercholesterolaemia Moderately common • Drugs: Diuretics Cyclosporin Glucocorticoids Androgens Antiretroviral agents • Hypothyroidism • Pregnancy • Cholestatic liver disease

Less common • Nephrotic syndrome • Anorexia nervosa • Porphyria • Hyperparathyroidism

Secondary hypertriglyceridaemia Common • Type 2 diabetes mellitus • Chronic renal disease • Abdominal obesity • Excess alcohol • Hepatocellular disease • Drugs: β -blockers Retinoids Glucocorticoids Antiretroviral agents

374 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE consanguineous marriage. Homozygosity results in more extensive xanthomas and precocious cardiovascular disease, often in

childhood. Hyperalphalipoproteinaemia refers to increased levels of HDL-C. In the absence of an increase in LDL-C, this condition rarely causes cardiovascular disease, but exceptions can occur so it should not be regarded as universally benign. Familial combined hyperlipidaemia, and dysbetalipoproteinaemia, may present with the pattern of predominant hypercholesterolaemia (see 'Mixed hyperlipidaemia' below). Hypertriglyceridaemia Hypertriglyceridaemia also usually involves polygenic factors (see Box 14.26). Other common causes include excess alcohol intake, medications (such as β -blockers and retinoids), type 2 diabetes, impaired glucose tolerance, central obesity or other manifestations of insulin resistance (p. 728) and impaired absorption of bile acids. It is often accompanied by post-prandial hyperlipidaemia and reduced HDL-C, both of which may contribute to cardiovascular risk. Excessive intake of alcohol or dietary fat, or other exacerbating factors, may precipitate a massive increase in TG levels, which, if they exceed 10 mmol/L (880 mg/dL), may pose a risk of acute pancreatitis. Monogenic forms of hypertriglyceridaemia also occur due to loss-of-function mutations in the genes encoding lipoprotein lipase, Apo C2 or ANGPTL4, which coordinate the lipolytic breakdown of TG-rich lipoproteins. These cause recessively inherited forms of severe hypertriglyceridaemia that is not readily amenable to drug treatment. They can present in childhood and may be associated with episodes of acute abdominal pain and pancreatitis. In common with other causes of severe hypertriglyceridaemia, hepatomegaly, lipaemia retinalis and eruptive xanthomas may occur (p. 346). Familial hypertriglyceridaemia may also be inherited in a dominant manner due to mutations in the APOA5 gene, which encodes Apo A5 – a co-factor that is essential for lipoprotein lipase activity. These disorders may also be associated with increased risk of cardiovascular disease. Familial combined hyperlipidaemia, and dysbetalipoproteinaemia, may present with the pattern of predominant hypertriglyceridaemia (see 'Mixed hyperlipidaemia', below). LDL-C (Box 14.26). Physical signs, such as corneal arcus and xanthelasma, may be found in this as well as other forms of lipid disturbance (p. 346). The risk of cardiovascular disease is proportional to the degree of LDL-C (or Apo B) elevation, but is modified by other major risk factors, including low HDL-C and high Lp(a). Familial hypercholesterolaemia (FH) is a more severe disorder with a prevalence of at least 0.4% in most populations. It is usually caused by loss-of-function mutations affecting the LDLR gene, which results in an autosomal dominant pattern of inheritance. A similar syndrome can arise with loss-of-function mutations in the ligand-binding domain of Apo B100 or gain-of-function mutations in PCSK9, which promote LDLR degradation. Causative mutations can be detected in one of these three genes by genetic testing in about 70% of patients with FH. Most patients with these types of FH have LDL-C levels that are approximately twice as high as in normal subjects of the same age and gender. Affected patients suffer from severe hypercholesterolaemia and premature cardiovascular disease. FH may be accompanied by xanthomas of the Achilles or extensor digitorum tendons (p. 346), which are strongly suggestive of FH. The onset of corneal arcus before age 40 is also suggestive of this condition. Identification of an index case of FH (the first case of FH in a family) should trigger genetic and biochemical screening of other family members, which is a cost-effective method for case detection. Affected individuals should be managed from childhood (Box 14.27). Homozygous FH may occur sporadically, especially in populations in which there is a 'founder' gene effect or 14.26 Classification of hyperlipidaemia

Disease	Elevated lipid results
Predominant hypercholesterolaemia	Polygenic (majority) TC $\pm$ TG LDL $\pm$ VLDL + – Familial hypercholesterolaemia (LDLR defect, defective Apo B100, increased function of PCSK9) TC $\pm$ TG LDL $\pm$ VLDL + + + –
Hyperalphalipoproteinaemia	TC $\pm$ TG HDL – –
Predominant hypertriglyceridaemia	Polygenic (majority) TG VLDL $\pm$ LDL Variable +
Lipoprotein lipase deficiency	TG $\nearrow$ TC Chylo ? + + +
Familial hypertriglyceridaemia	TG > TC VLDL $\pm$

Chylo ? ++ Mixed hyperlipidaemia Polygenic (majority) TC + TG VLDL + LDL Variable + Familial combined hyperlipidaemia* TC and/or TG LDL and/or VLDL ++ + Dysbetalipoproteinaemia* TC and/or TG IDL +++ +

- = slightly increased risk; ++ = increased risk; +++ = greatly increased risk; ? = risk unclear
- *Familial combined hyperlipidaemia and dysbetalipoproteinaemia may also present as predominant hypercholesterolaemia or predominant hypertriglyceridaemia.
- (Apo B100 = apolipoprotein B100; CHD = coronary heart disease; Chylo = chylomicrons; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; LDLR = low-density lipoprotein receptor; TC = total cholesterol; TG = triglycerides; VLDL = very low-density lipoprotein)
- 14.27 Familial hypercholesterolaemia in adolescence
- Statin treatment: may be required from the age of about 10. It does not compromise normal growth and maturation.
- Smoking: patients should be strongly advised not to smoke.
- Adherence to medication: critically important to the success of treatment. Simple regimens should be used and education and support provided.

Lipids and lipoprotein metabolism • 375

Fish eye disease, Apo A1 Milano and lecithin cholesterol acyl transferase (LCAT) deficiency demonstrate that very low HDL-C levels do not necessarily cause cardiovascular disease, but Apo A1 deficiency, and possibly Tangier disease, demonstrate that low HDL-C can be atherogenic under some circumstances. Autosomal recessive FH and PCSK9 gain-of-function mutations reveal the importance of proteins that chaperone the LDLR. Sitosterolaemia and cerebrotendinous xanthomatosis demonstrate that sterols other than cholesterol can cause xanthomas and cardiovascular disease, while PCSK9 loss-of-function mutations, abetalipoproteinaemia and hypobetalipoproteinaemia suggest that low levels of Apo B-containing lipoproteins reduce the risk of cardiovascular disease. The only adverse health outcomes associated with extremely low plasma lipid levels in the latter two conditions are attributable to fat-soluble vitamin deficiency, or impaired transport of lipid from intestine or liver.

Principles of management Lipid-lowering therapies have a key role in the secondary and primary prevention of cardiovascular diseases (p. 487). Assessment of absolute risk of cardiovascular disease, treatment of all modifiable risk factors and optimisation of lifestyle, especially diet and exercise, are central to management in all cases. Patients with the greatest absolute risk of cardiovascular disease derive the greatest absolute benefit from treatment. Public health organisations recommend thresholds for the introduction of lipid-lowering therapy based on the identification of patients in very high-risk categories, or those calculated to be at high absolute risk according to algorithms or tables such as the Joint British Societies Coronary Risk Prediction Chart (see Fig. 16.77, p. 511). These tables, which are based on large epidemiological studies, should be recalibrated for the local population, if possible. In general, patients who have cardiovascular disease, diabetes mellitus, chronic renal impairment, familial hypercholesterolaemia or an absolute risk of cardiovascular disease of more than 20% in the ensuing 10 years are arbitrarily regarded as having sufficient risk to justify drug treatment. Age is such an overwhelming determinant of absolute cardiovascular risk that some recent recommendations consider 'lifetime' risk. This diminishes the pressure to treat very elderly patients and supports earlier intervention in non-elderly patients. Public health organisations also recommend target levels for patients receiving drug treatment. High-risk patients should aim for HDL-C > 1 mmol/L (38 mg/dL) and fasting TG < 2 mmol/L (approximately 180 mg/dL), while target

levels for LDL-C have been reduced to 1.8 mmol/L (76 mg/dL) or less. In general, total cholesterol should be < 5 mmol/L (190 mg/dL) during treatment, and < 4 mmol/L (approximately 150 mg/dL) in high-risk patients and in secondary prevention of cardiovascular disease. Recent trials have demonstrated continuous benefit of LDL-C reduction to a level of 1.4 mmol/L (54 mg/dL), so further reduction in treatment targets may be anticipated. Non-pharmacological management Patients with lipid abnormalities should receive medical advice and, if necessary, dietary counselling to:

- reduce intake of saturated and trans-unsaturated fat to less than 7–10% of total energy
- reduce intake of cholesterol to < 250 mg/day
- replace sources of saturated fat and cholesterol with alternative foods, such as lean meat, low-fat dairy

Mixed hyperlipidaemia It is difficult to define quantitatively the distinction between predominant hyperlipidaemias and mixed hyperlipidaemia. The term 'mixed' usually implies the presence of hypertriglyceridaemia, as well as an increase in LDL-C or IDL. Treatment of massive hypertriglyceridaemia may improve TG faster than cholesterol, thus temporarily mimicking mixed hyperlipidaemia. Primary mixed hyperlipidaemia is usually polygenic and, like predominant hypertriglyceridaemia, often occurs in association with type 2 diabetes, impaired glucose tolerance, central obesity or other manifestations of insulin resistance (p. 728). Both components of mixed hyperlipidaemia may contribute to the risk of cardiovascular disease. Familial combined hyperlipidaemia is a term used to identify an inherited tendency towards the over-production of atherogenic Apo B-containing lipoproteins. It results in elevation of cholesterol, TG or both in different family members at different times. It is associated with an increased risk of cardiovascular disease but it does not produce any pathognomonic physical signs. In practice, this relatively common condition is substantially modified by factors such as age and weight. It may not be a monogenic condition, but rather one end of a heterogeneous spectrum that overlaps insulin resistance. **Dysbetalipoproteinaemia** (also referred to as type 3 hyperlipidaemia, broad-beta dyslipoproteinaemia or remnant hyperlipidaemia) involves accumulation of roughly equimolar levels of cholesterol and TG. It is caused by homozygous inheritance of the Apo E2 allele, which is the isoform least avidly recognised by the LDLR. In conjunction with other exacerbating factors, such as obesity or diabetes, it leads to accumulation of atherogenic IDL and chylomicron remnants. Premature cardiovascular disease is common, as is peripheral vascular disease. It may also result in the formation of palmar xanthomas, tuberous xanthomas or tendon xanthomas. **Rare dyslipidaemias** Several rare disturbances of lipid metabolism have been described (Box 14.28). They provide important insights into lipid metabolism and its impact on risk of cardiovascular disease.

14.28 Miscellaneous and rare forms of hyperlipidaemia

Condition	Lipoprotein pattern	CVD risk
Tangier disease	Very low HDL, low TC + Apo A1 deficiency	Very low HDL ++ Apo A1
Milano	Very low HDL –	Fish eye disease
Very low HDL, high TG –	LCAT deficiency	Very low HDL, high TG ?
Autosomal recessive FH	Very high LDL ++	Sitosterolaemia
High plant sterols including sitosterol +	Cerebrotendinous xanthomatosis	Bile acid defect (cholestanol accumulation) +

- = slightly increased risk; ++ = increased risk. (CVD = cardiovascular disease; FH = familial hypercholesterolaemia; HDL = high-density lipoprotein; LCAT = lecithin cholesterol acyl transferase; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides)

376 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE of LDL and its precursor, IDL, resulting in a secondary reduction in LDL synthesis. Statins reduce LDL-C by up to 60%, reduce TG by up to 40% and increase HDL-C by up to 10%. They also reduce the concentration of intermediate metabolites such as isoprenes, which may lead to other effects such as suppression of the

inflammatory response. There is clear evidence of protection against total and coronary mortality, stroke and cardiovascular events across the spectrum of cardiovascular disease risk. Statins are generally well tolerated and serious side-effects are rare (well below 2%). Liver function test abnormalities and muscle problems, such as myalgia, asymptomatic increase in creatine kinase (CK), myositis and, infrequently, rhabdomyolysis, are the most common. Side-effects are more likely in patients who are elderly, debilitated or receiving other drugs that interfere with statin degradation, which usually involves cytochrome P450 3A4 or glucuronidation. Ezetimibe inhibits activity of the intestinal mucosal transporter NPC1L1, which is responsible for absorption of dietary and biliary cholesterol. The resulting depletion of hepatic cholesterol up-regulates hepatic LDLR production. This mechanism of action is synergistic with the effect of statins. Monotherapy in a 10 mg/day dose reduces LDL-C by 15–20%. Slightly greater (17–25%) incremental LDL-C reduction occurs when ezetimibe is added to statins. Ezetimibe is well tolerated, and evidence of a beneficial effect on cardiovascular disease endpoints is now available. Plant sterol-supplemented foods, which also reduce cholesterol absorption, lower LDL-C by 7–15%. Bile acid-sequestering resins. Drugs in this class include colestyramine, colestipol and colesevelam. These prevent the reabsorption of bile acids, thereby increasing de novo bile acid synthesis from hepatic cholesterol. As with ezetimibe, the resultant depletion of hepatic cholesterol up-regulates LDL receptor activity and reduces LDL-C in a manner that is synergistic with the action of statins. Resins reduce LDL-C and modestly increase HDL-C, but may increase TG. They are safe but may interfere with bioavailability of other drugs. Colesevelam has fewer gastrointestinal effects than older products.

• reduce energy-dense foods such as fats and soft drinks, while increasing activity and exercise to maintain or lose weight

• increase consumption of cardioprotective and nutrient-dense foods, such as vegetables, unrefined carbohydrates, fish, pulses, nuts, legumes, and fruit

• adjust alcohol consumption, reducing intake if excessive or if associated with hypertension, hypertriglyceridaemia or central obesity

• achieve additional benefits with preferential intake of foods containing lipid-lowering nutrients such as n-3 fatty acids, dietary fibre and plant sterols. The response to diet is usually apparent within 3–4 weeks but dietary adjustment may need to be introduced gradually. Although hyperlipidaemia in general, and hypertriglyceridaemia in particular, can be very responsive to these measures, LDL-C reductions are often only modest in routine clinical practice. Explanation, encouragement and persistence are often required to assist patient adherence. Even minor weight loss can substantially reduce cardiovascular risk, especially in centrally obese patients (p. 700). All other modifiable cardiovascular risk factors should be assessed and treated. If possible, intercurrent drug treatments that adversely affect the lipid profile should be replaced. Pharmacological management

The main diagnostic categories provide a useful framework for management and the selection of first-line pharmacological treatment (Fig. 14.14). Hypercholesterolaemia Hypercholesterolaemia can be treated with one or more of the cholesterol-lowering drugs as described below. Statins These reduce cholesterol synthesis by inhibiting the HMGCoA reductase enzyme. The reduction in cholesterol synthesis up-regulates production of the LDLR, which increases clearance Fig. 14.14

Flow chart for the drug treatment of hyperlipidaemia. *Interrupt treatment if creatine kinase is more than 5–10 times the upper limit of normal, or if elevated with muscle symptoms, or if alanine aminotransferase is more than 2–3 times the upper limit. To convert triglyceride (TG) in mmol/L to mg/dL, multiply by 88. To convert low-density lipoprotein (LDL)-C in mmol/L to mg/dL, multiply by 38.*

Predominant hypercholesterolaemia Mixed hyperlipidaemia Predominant hypertriglyceridaemia

First-line treatment with statin Ezetimibe if intolerant Monitor lipids, Monitor for side-effects Titrate dose Statin ± ezetimibe ± resin ± nicotinate if resistant Combination treatment if TG and LDL > 4

mmol/L Statin + fish oil Fibrate + ezetimibe Statin + nicotinate Statin + fibrate Monitor for side-effects* First-line treatment with fibrate Fish oil if intolerant Monitor lipids, Monitor for side-effects* Titrate fish oil Fibrate ± fish oil ± nicotinate if resistant

Lipids and lipoprotein metabolism • 377

Highly polyunsaturated long-chain n-3 fatty acids These include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which comprise approximately 30% of the fatty acids in fish oil. EPA and DHA are potent inhibitors of VLDL TG formation. Intakes of more than 2 g n-3 fatty acid (equivalent to 6 g of most forms of fish oil) per day lower TG in a dose-dependent fashion. Up to 50% reduction in TG may be achieved with 15 g fish oil per day. Changes in HDL-C are variable but fish oils do not routinely reduce LDL-C. Fish oil fatty acids have also been shown to inhibit platelet aggregation and improve cardiac arrhythmia in animal models. Dietary and pharmacological trials suggested that n-3 fatty acids may reduce mortality from coronary heart disease, but the benefit of fish oil supplements has been less conclusive in recent trials. Fish oils appear to be safe and well tolerated but dietary fish consumption is the preferred source. Patients with predominant hypertriglyceridaemia who do not respond to lifestyle intervention can be treated with fibrates or fish oil, depending on individual response and tolerance. If target levels are not achieved, the fibrates, fish oil and possibly nicotinic acid can be combined. Massive hypertriglyceridaemia may require more aggressive limitation of dietary fat intake (< 10–20% energy as fat). Any degree of insulin deficiency should be corrected because insulin is required for optimal activity of lipoprotein lipase. The initial target for patients with massive hypertriglyceridaemia is TG < 10 mmol/L (880 mg/dL), to reduce the risk of acute pancreatitis. Mixed hyperlipidaemia Mixed hyperlipidaemia can be difficult to treat. First-line therapy with statins alone is unlikely to achieve target levels once fasting TGs exceed approximately 4 mmol/L (350 mg/dL). Fibrates preparations that are less well tolerated. The depletion of bile acids is sensed via the farnesyl X receptor and the response may also improve glucose metabolism. PCSK9 inhibitors Monoclonal antibodies have been developed that neutralise PCSK9, an enzyme that degrades the LDLR. This causes levels of LDLR to increase, which markedly reduces LDL-C. The PCSK9 inhibitors currently available are evolocumab and alirocumab, which are administered by subcutaneous injection every 2–4 weeks. These drugs are well tolerated and highly effective. Reductions in LDL-C of about 50–60% have been observed in patients who have not responded adequately to standard lipid-lowering therapy and this has been accompanied by a reduction in the risk of cardiovascular events of about 15%. The PCSK9 inhibitors do not deplete intracellular concentrations and, because of that, do not trigger compensatory mechanisms that blunt the effect of other cholesterol-lowering medications. Nicotinic acid Pharmacological doses reduce peripheral fatty acid release, with the result that VLDL and LDL decline while HDL-C increases. Recent randomised clinical trials have been disappointing regarding effects on atherosclerosis and cardiovascular events. The same may be said of novel agents that inhibit cholesterol ester transfer protein. Neither of these HDL-C-raising drugs is indicated in current lipid management. Combination therapy In many patients, treatment of predominant hypercholesterolaemia can be achieved by diet plus the use of a statin in sufficient doses to achieve target LDL-C levels. Patients who do not reach LDL targets on the highest tolerated statin dose, or who are intolerant of statins, may receive ezetimibe, plant sterols, or resins. Ezetimibe and resins are safe and effective in combination with a statin because the mechanisms of action of individual therapies complement each other while blunting each other's compensatory mechanisms. Hypertriglyceridaemia Predominant hypertriglyceridaemia can be

treated with one of the TG-lowering drugs described below (see Fig. 14.14). Fibrates These stimulate peroxisome proliferator-activated receptor (PPAR) α , which controls the expression of gene products that mediate the metabolism of TG and HDL. As a result, synthesis of fatty acids, TG and VLDL is reduced, while that of lipoprotein lipase, which catabolises TG, is enhanced. In addition, production of Apo A1 and ABC A1 is up-regulated, leading to increased reverse cholesterol transport via HDL. Consequently, fibrates reduce TG by up to 50% and increase HDL-C by up to 20%, but LDL-C changes are variable. Fewer large-scale trials have been conducted with fibrates than with statins. The results are less conclusive, but reduced rates of cardiovascular disease have been reported with fibrate therapy in the subgroup of patients with low HDL-C levels and elevated TG (TG > 2.3 mmol/L (200 mg/dL)). Fibrates are usually well tolerated but share a similar side-effect profile to statins. In addition, they may increase the risk of cholelithiasis and prolong the action of anticoagulants. Accumulating evidence suggests that they may also have a protective effect against diabetic microvascular complications.

14.29 Management of hyperlipidaemia in old age

- Prevalence of atherosclerotic cardiovascular disease: greatest in old age.
- Associated cardiovascular risk: lipid levels become less predictive, as do other risk factors apart from age itself.
- Benefit of statin therapy: maintained up to the age of 80 years but evidence is lacking beyond this.
- Life expectancy and statin therapy: lives saved by intervention are associated with shorter life expectancy than in younger patients, and so the impact of statins on quality-adjusted life years is smaller in old age.

14.30 Dyslipidaemia in pregnancy

- Lipid metabolism: lipid and lipoprotein levels increase during pregnancy. This includes an increase in low-density lipoprotein cholesterol, which resolves post-partum. Remnant dyslipidaemia and hypertriglyceridaemia may be exacerbated during pregnancy.
- Treatment: dyslipidaemia is rarely thought to warrant urgent treatment so pharmacological therapy is usually contraindicated when conception or pregnancy is anticipated. Teratogenicity has been reported with systemically absorbed agents, and non-absorbed agents may interfere with nutrient bioavailability.
- Monitoring: while still uncommon among women of child-bearing age, cardiovascular disease is increasing in prevalence. Preconception cardiovascular review should be considered for women at high risk to optimise medications for pregnancy and to ensure that the patient will be able to withstand the demands of pregnancy and labour.

378 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE combination with fibrates, or other drugs that may interfere with their clearance. If myalgia or weakness occurs in association with CK elevation over 5–10 times the upper limit of normal, or if sustained alanine aminotransferase (ALT) elevation more than 2–3 times the upper limit of normal occurs that is not accounted for by fatty liver (p. 882), treatment should be discontinued and alternative therapy sought. The principles of the management of dyslipidaemia can be applied broadly, but the objectives of treatment in the elderly (Box 14.29) and the safety of pharmacological therapy in pregnancy (Box 14.30) warrant special consideration.

The porphyrias This group of disorders is caused by inherited abnormalities in the haem biosynthetic pathway (Fig. 14.15). Most of the described forms are due to partial enzyme deficiencies with a dominant mode of inheritance. They are commonly classified as hepatic or erythropoietic, depending on whether the major site of excess porphyrin production is in the liver or red cell. The porphyrias have a penetrance in the order of 25%, emphasising the importance of environmental factors in disease expression. In porphyria cutanea tarda (PCT), which is the most common, first-line therapy for dysbetalipoproteinaemia, but they may not control the cholesterol component in other forms of mixed hyperlipidaemia. Combination therapy is often required. Effective combinations include:

- statin plus fenofibrate (recognising that the risk of

myopathy is increased with gemfibrozil, but fenofibrate is relatively safe in this regard) • statin plus fish oil when TG is not too high • fibrate plus ezetimibe when cholesterol is not too high. Monitoring of therapy The effects of lipid-lowering therapy should be assessed after 6 weeks (12 weeks for fibrates). At this point, it is prudent to review side-effects, lipid response (see target levels above), CK and liver function tests. During longer-term follow-up, adherence to treatment, diet and exercise should be assessed, with monitoring of weight, blood pressure and lipid levels. The presence of cardiovascular symptoms or signs should be noted and absolute cardiovascular risk assessed periodically. Effective statin therapy may be associated with a paradoxical and as yet unexplained increase in coronary calcium score. It is not necessary to perform routine checks of CK and liver function unless symptoms occur, or if statins are used in Fig. 14.15 Haem biosynthetic pathway and enzyme defects responsible for the porphyrias. (ALA = δ -aminolaevulinic acid; CoA = co-enzyme A; N = neurovisceral; P = photosensitive; PBG = porphobilinogen) δ -aminolaevulinic acid (ALA) Porphobilinogen (PBG) Hydroxymethylbilane Uroporphyrinogen III Coproporphyrinogen III Protoporphyrinogen IX Protoporphyrin IX (proto IX) Haem ALA dehydratase Coproporphyrin I (Copro I) Uroporphyrin I (Uro I) Isocoproporphyrin (Isocopro) Coproporphyrin III (Copro III) Plumboporphyria PBG deaminase Acute intermittent porphyria Uroporphyrinogen synthetase Congenital erythropoietic porphyria Uroporphyrinogen decarboxylase Porphyria cutanea tarda Coproporphyrinogen oxidase Hereditary coproporphyria Protoporphyrinogen oxidase Variegate porphyria Ferrochelatase Erythropoietic protoporphyria +Fe²⁺ N N P P N + P P N + P Pathway Metabolites Enzyme Deficiency disease Symptomatology Glycine + succinyl CoA

The porphyrias • 379

difficult to obtain suitable specimens for analysis. All the genes of the haem biosynthetic pathway have now been characterised. This has made it possible to identify affected individuals in families by genetic testing, a significant advance considering that penetrance of porphyria is low. Metabolite excretory patterns are always grossly abnormal during an acute attack or with cutaneous manifestations of porphyria, and are diagnostic of the particular porphyria. A normal metabolite profile under these circumstances effectively excludes porphyria. Metabolites usually remain abnormal for long periods after an acute attack, and in some individuals never return to normal. The diagnosis is not so straightforward in patients who are in remission, or in asymptomatic individuals with a positive family history. Neurological porphyria rarely manifests before puberty, nor can it be readily diagnosed after the menopause as porphyrin excretion may be normal. Genetic testing for disease-specific mutations can clarify the situation. Management For patients predisposed to neurovisceral attacks, general management includes avoidance of any agents known to precipitate acute porphyria. Specific management includes intravenous glucose, as provision of 5000 kilojoules per day can, in some cases, terminate acute attacks through a reduction in δ -aminolaevulinic acid (ALA) synthetase activity, leading to reduced ALA and porphyrin synthesis. More recently, administration of haem (in various forms such as haematin or haem arginate) has been shown to reduce metabolite excretory rates, relieve pain and accelerate recovery. Cyclical acute attacks in women sometimes respond to suppression of the menstrual cycle using gonadotrophin-releasing hormone analogues. In rare cases with frequent prolonged attacks or attacks intractable to treatment, liver transplantation has been effective. There are few specific or effective measures to treat the photosensitive manifestations. The primary goal is to avoid sun exposure and skin trauma. Barrier sun creams containing zinc or titanium oxide are the most effective products. New colourless creams containing nanoparticle formulations have

improved patient acceptance. Beta-carotene is used in some patients with erythropoietic porphyria with some efficacy. Afamelanotide, a synthetic analogue of alpha-melanocyte stimulating hormone (α MSH), has also been shown to provide protection in erythropoietic protoporphyria, and is now undergoing approval in many countries. In porphyria cutanea tarda, a course of venesections to remove iron can result in long-lasting clinical and biochemical remission, common cause of porphyria, environmental triggers include alcohol, iron accumulation, exogenous oestrogens and exposure to various chemicals. Many cases are associated with hepatitis C infection and this should always be screened for on presentation. Clinical features The clinical features of porphyria fall into two broad categories: photosensitivity and acute neurovisceral syndrome. The enzyme defects responsible for the diseases are shown in Figure 14.15. Photosensitive skin manifestations, attributable to excess production and accumulation of porphyrins in the skin, cause pain, erythema, bullae, skin erosions, hirsutism and hyperpigmentation, and occur predominantly on areas of the skin that are exposed to sunlight (p. 1220). The skin also becomes sensitised to damage from minimal trauma. The other pattern of presentation is with an acute neurological syndrome. This almost always presents with acute abdominal pain together with features of autonomic dysfunction, such as tachycardia, hypertension and constipation. Neuropsychiatric manifestations, hyponatraemia due to inappropriate ADH release (p. 357), and an acute neuropathy may also occur (p. 1138). The neuropathy is predominantly motor and may, in severe cases, progress to respiratory failure. There is no proven explanation for the episodic nature of the attacks in porphyria, which can relapse and remit or follow a prolonged and unremitting course. Sometimes, specific triggers can be identified, such as alcohol, fasting, or drugs such as anticonvulsants, sulphonamides, oestrogen and progesterone. The oral contraceptive pill is a common precipitating factor. In a significant number, no precipitant can be identified.

Investigations The diagnosis of porphyria and classification into the various forms have traditionally relied on measurements of porphyrins and porphyrin precursors found in blood, urine and faeces (Box 14.31). The diagnosis is straightforward when the metabolites are significantly elevated, but this is not always the case in asymptomatic individuals who may have normal porphyrin studies. More recently, measurement of the enzymes that are deficient in the various porphyrias has provided further diagnostic information. An example is measurement of porphobilinogen deaminase activity in red blood cells to diagnose acute intermittent porphyria. There is often considerable overlap between enzyme activities in affected and normal subjects, however. Furthermore, some of the enzymes occur in the mitochondria, for which it is more difficult to measure.

14.31 Diagnostic biochemical findings in the porphyrias

Condition	Blood	Urine	Faeces
ALA dehydratase deficiency (plumboporphyria)	Elevated	Elevated	Elevated
Acute intermittent porphyria (AIP)	Elevated	Elevated	Elevated
Congenital erythropoietic porphyria (CEP)	Elevated	Elevated	Elevated
Porphyria cutanea tarda (PCT)	Elevated	Elevated	Elevated
Hereditary coproporphyria (HCP)	Elevated	Elevated	Elevated
Variegate porphyria (VP)	Elevated	Elevated	Elevated
Erythropoietic protoporphyria (EPP)	Elevated	Elevated	Elevated

Refer to Figure 14.15 for metabolic pathways. The paradoxical rise in coproporphyrin III (Copro III) and protoporphyrin (Proto) in this very rare condition is poorly understood. (ALA = δ -aminolaevulinic acid; Isocopro = isocoproporphyrin; PBG = porphobilinogen; Uro = uroporphyrin)

380 • CLINICAL BIOCHEMISTRY AND METABOLIC MEDICINE especially if exposure to identified precipitants, such as alcohol or oestrogens, is reduced. Alternatively, a prolonged course of low-dose chloroquine therapy is effective. Further information Journal articles Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol* 2014; 170:G1-G47. Walsh S, Unwin R. Renal tubular disorders. *Clin Med* 2012; 12(5):476-479. Websites emedicine.medscape.com The Nephrology link on this site contains a

useful compendium of articles. lipidsonline.org Summarises management strategies for dyslipidaemia. ncbi.nlm.nih.gov The link to OMIM (Online Mendelian Inheritance in Man) provides updated information on the genetic basis of metabolic disorders. porphyria-europe.com and drugs-porphyria.org Excellent resources on drug safety in porphyria.

Revision #1

Created 2026-01-08 16:24:43 UTC by Omar Ayman

Updated 2026-01-08 16:24:43 UTC by Omar Ayman