CHAPTER

74 Fluid–Electrolyte and Acid–Base Disorders Complicating Diabetes Mellitus

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Diabetes mellitus, the most prevalent endocrine disorder, is a very challenging condition responsible for the development of severe abnormalities in whole body composition and damage of critical functions. The deranged metabolic pathways lead to defects in the normal fluid–electrolyte and acid–base homeostasis, which are reviewed in this chapter. We examine the basic defects of diabetes mellitus, and describe each of the various disturbances of water, electrolyte, and acid–base composition observed in association with this disease.

KETOSIS AND KETOACIDOSIS

Ketosis is an abnormal state of nutrient metabolism that develops when the rate of production of ketones exceeds their removal; as a result, ketones accumulate in body fluids as reflected by high blood and urine levels.[1–4] Because ketones are largely organic acids (β-hydroxybutyric and acetoacetic acid) that dissociate almost completely at the pH of the body fluids, their production generates H^+ ions, which consume HCO_3^- and lead to metabolic acidosis (ketoacidosis). The term ketosis is used to describe a mild form of the disturbance, reserving the term ketoacidosis for the full-blown condition that features substantial metabolic acidosis.[5]

The mechanisms underlying ketoacidosis are essentially the same whether it develops as an acute complication of diabetes mellitus or in nondiabetic subjects (e.g., starvation ketosis, alchoholic ketoacidosis). Abnormal levels or action of insulin and glucagon are required for the development of ketosis.[5–10] Insulin deficiency or resistance impairs glucose utilization in skeletal muscle and increases adipose tissue and muscle breakdown, thereby augmenting delivery of glycerol and alanine (gluconeogenic substrates) to the liver. Hepatic gluconeogenesis, in turn, is stimulated by insulin deficiency and, more importantly, by glucagon excess. The fatty acids released from the enhanced lipolysis are converted to ketones by the hepatocytes under the influence of glucagon excess. Pancreatic β cell destruction is largely responsible for the hormonal imbalance observed in most cases of diabetic ketoacidosis. Conversely, insulin deficiency in the presence of normal β cells plays a major role in ketosis associated with fasting, starvation, ethanol ingestion, and some liver diseases.

Diabetic ketoacidosis (DKA) is a disease state characterized by the presence of hyperglycemia and hyperosmolality, metabolic acidosis due to ketoacid accumulation, extracellular and intracellular fluid depletion, and varying degrees of electrolyte deficiency, particularly of potassium and phosphate.[9–11]

ROLES OF INSULIN AND GLUCAGON

In normal fasting individuals, the major source of glucose (approximately 90%) is from the liver, through glycogenolysis and gluconeogenesis. The kidney contributes the remaining 10% through synthesis of glucose from three-carbon precursors (gluconeogenesis). After a meal, glucose absorption increases the plasma glucose level. The resultant hyperglycemia-induced stimulation of insulin secretion suppresses hepatic glucose production, largely through inhibition of glycogenolysis, and stimulates glucose uptake by the liver, the gut, and peripheral tissues, including skeletal muscle.

The abnormal metabolism of carbohydrates and lipids observed in DKA is largely caused by a rise in the molar ratio of glucagon/insulin in plasma. The two hormones are metabolic antagonists with respect to fuel production and utilization but their primary effects occur on different tissues. Insulin acts on muscle and adipose tissue augmenting glucose transport and inhibiting lipolysis. Conversely, glucagon primarily acts on the liver increasing glycogenolysis, gluconeogenesis, and ketogenesis. Insulin's action on the hepatocyte is essentially that of an antiglucagon hormone, as it has minimal hepatic effects in the absence of glucagon-induced metabolic changes. Insulin decreases glucagon release from α cells in the pancreatic islets and inhibits a glucagon-activated, cAMP-dependent protein kinase in the hepatocyte.[5] Beyond the critical role of glucagon in ketone body production, other hormones, including catecholamines, cortisol, growth hormones, and thyroid hormones, increase hepatic ketogenesis and may participate in the pathogenesis of diabetic ketoacidosis (Fig. 74.1).[12]

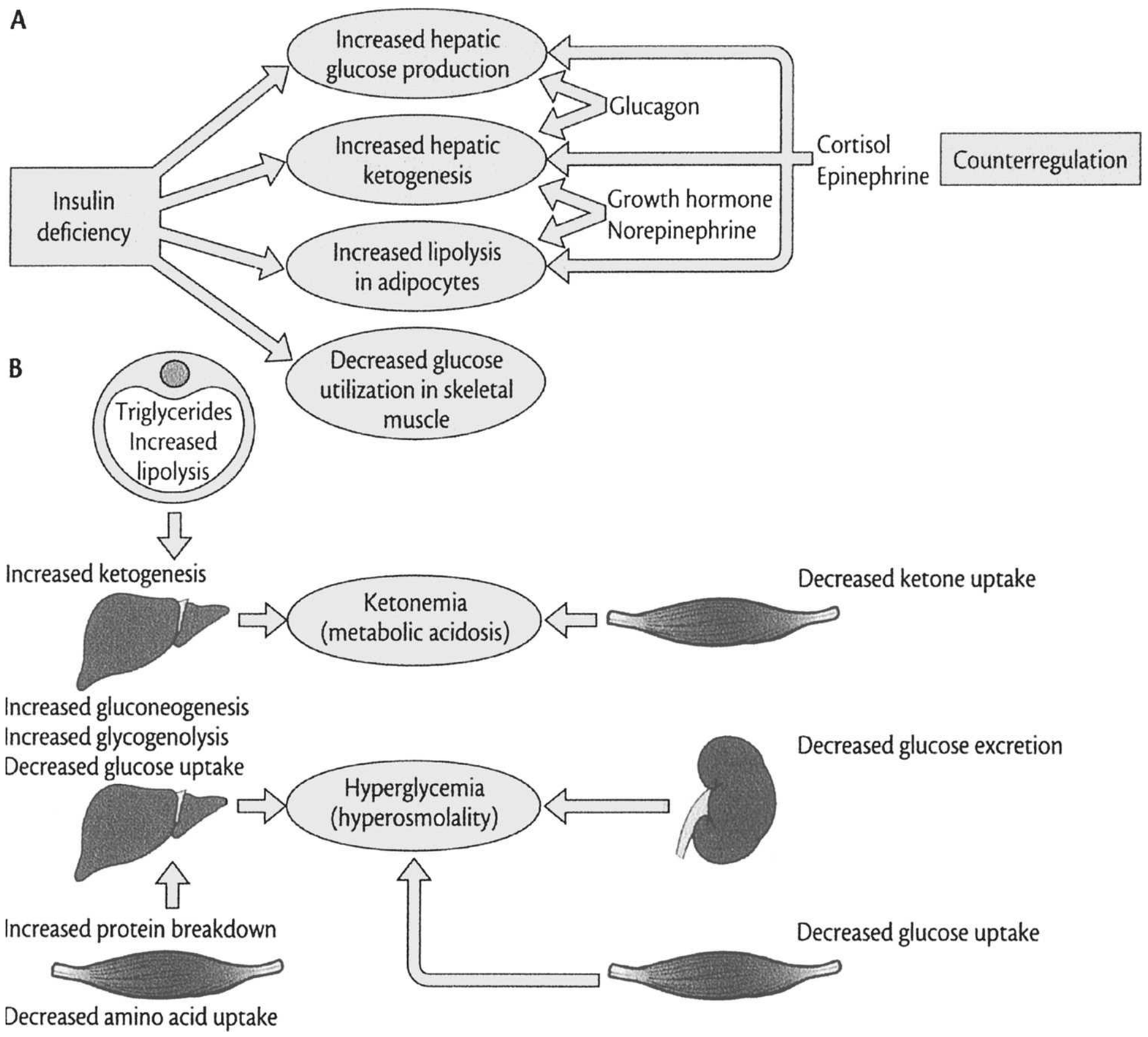

FIGURE 74.1 Role of insulin deficiency, counterregulatory hormones, and various tissues and organs in the pathogenesis of hyperglycemia and ketosis in diabetic ketoacidosis (DKA). **A:** Metabolic processes affected by insulin deficiency, on the one hand, and excess of glucagon, cortisol, epinephrine, norepinephrine, and growth hormone, on the other. **B:** The roles of the adipose tissue, liver, skeletal muscle, and kidney in the pathogenesis of hyperglycemia and ketonemia. Excessive hepatic production of glucose and impairment of glucose utilization are the main determinants of hyperglycemia. Increased hepatic production of ketones and their reduced utilization by peripheral tissues account for the ketonemia. (From Adrogué HJ, Madias NE. Disorders of acid–base balance. In: Berl T, Bonventre JV, eds. *Atlas of Diseases of the Kidney*. Boston: Blackwell Scientific; 1999.)

DISTURBANCES IN BODY COMPOSITION

The major fluid–electrolyte and acid–base disorders complicating diabetes mellitus are conveniently classified as single disturbances and combinations of multiple disturbances (Table 74.1). Each of the single disturbances, including defects in homeostasis of glucose, lipids, water, sodium, potassium, phosphate, and acid–base balance, is characterized by unique features that are reviewed in this section. Combinations of multiple disturbances comprising the simultaneous presence of defects in the homeostasis of glucose, fluid, electrolyte, and acid–base balance are responsible for the development of the full-blown clinical pictures of diabetic ketoacidosis, nonketotic hyperglycemia (NKH), and renal failure complicating diabetes mellitus. These combined disturbances are examined thereafter, with the exception of renal failure, which is discussed elsewhere.

Single Disturbances

Defect in Glucose Homeostasis

In uncontrolled diabetes, hyperglycemia is caused by increased hepatic and renal glucose production and decreased glucose utilization in muscle and adipose tissue. Decreased glucose utilization, once considered the major contributor to hyperglycemia in uncontrolled diabetes, is currently believed to play a smaller role than excessive glucose production. Figure 74.2 depicts the hepatic and renal contribution to endogenous glucose production in conscious normal and diabetic dogs.[13] The rise in the glucagon/insulin ratio in plasma characteristic of uncontrolled diabetes activates key enzymes that accelerate the rates of both glycogenolysis and gluconeogenesis. The increased ratio also promotes glucose overproduction by modulating the effects of other hormones, availability of substrate, and rates of fatty acid oxidation (Fig. 74.1). Volume depletion secondary to hyperglycemia-induced osmotic diuresis reduces the urinary loss of glucose, thereby worsening hyperglycemia.

An important contributor to the development of hyperglycemia in uncontrolled diabetes may be the prevailing acidemia.[14–18] In animals with hypercapnia-induced acidemia, for example, a substantially smaller glucose infusion rate maintains euglycemia as compared to dogs without respiratory acidosis during constant insulin infusion, reflecting less glucose entry into cells for a given insulin level (Fig. 74.3).[19] Although the sympathetic surge characteristic of acidemia undoubtedly contributes to glucose intolerance, adrenergic blockade during acute respiratory acidosis does not prevent the disturbed glucoregulation. Nor do plasma levels of insulin fall during acute respiratory acidosis. In fact, acidemia reduces tissue extraction of insulin and, more specifically,

74.1 Major Fluid–Electrolyte and Acid–Base Disorders Complicating Diabetes Mellitus

Condition	Defect in Homeostasis of	Specific Entity
Single disturbance	Glucose	Hyponatremia (hypertonic or translocational)
		Hypernatremia
	Lipids	Pseudohyponatremia
	Water	Hyponatremia (hypotonic)
		Hypernatremia
	Sodium	Volume depletion
		Volume expansion
	Potassium	Hypokalemia, K^+ depletion
		Hyperkalemia
	Acid–base balance	Ketoacidosis
		Hyperchloremic acidosis
		Renal tubular acidosis
		Lactic acidosis
Combination of multiple disturbances	Glucose, fluid, and acid–base balance	Diabetic ketoacidosis
		Hyperosmolar nonketotic syndrome
		Renal failure

insulin uptake by the liver.[19] Although plasma glucagon levels also increase during metabolic or respiratory acidosis, the glucagon/insulin ratio in the portal circulation remains unchanged, thereby reducing the possible role of glucagon in the hyperglycemia of acidemic states. The weight of the evidence suggests that the hyperglycemia of acidemia is mediated by reduction of insulin binding to its receptor and decreased tissue sensitivity to the hormone.[19–22]

The defect in glucose homeostasis observed in uncontrolled diabetes might lead to either hyponatremia or hypernatremia.[23–25] The hyperglycemia-induced increase in effective osmotic pressure of the extracellular fluid (ECF) triggers a shift of water out of cells, most prominently skeletal muscle, which reduces serum $[Na^+]$. An increase of 100 mg per dL (5.6 mmol per L) in the glucose concentration decreases serum $[Na^+]$ by approximately 1.7 mEq per L, the end result being a rise in serum osmolality by approximately 2.0 mOsm per kg H_2O.[25,26] The resulting ECF expansion is, however, brief due to simultaneous renal and extrarenal loss of fluids. The hyperglycemia-induced increase in the filtered load of glucose exceeds the renal tubular reabsorptive capacity resulting in substantial glucosuria—one of the hallmarks of DKA. In turn, glucosuria causes osmotic diuresis that results in urinary losses of 75 to 150 mL per kg of water and 7 to 10 mEq per kg of Na^+ and Cl^- over an entire episode of DKA.

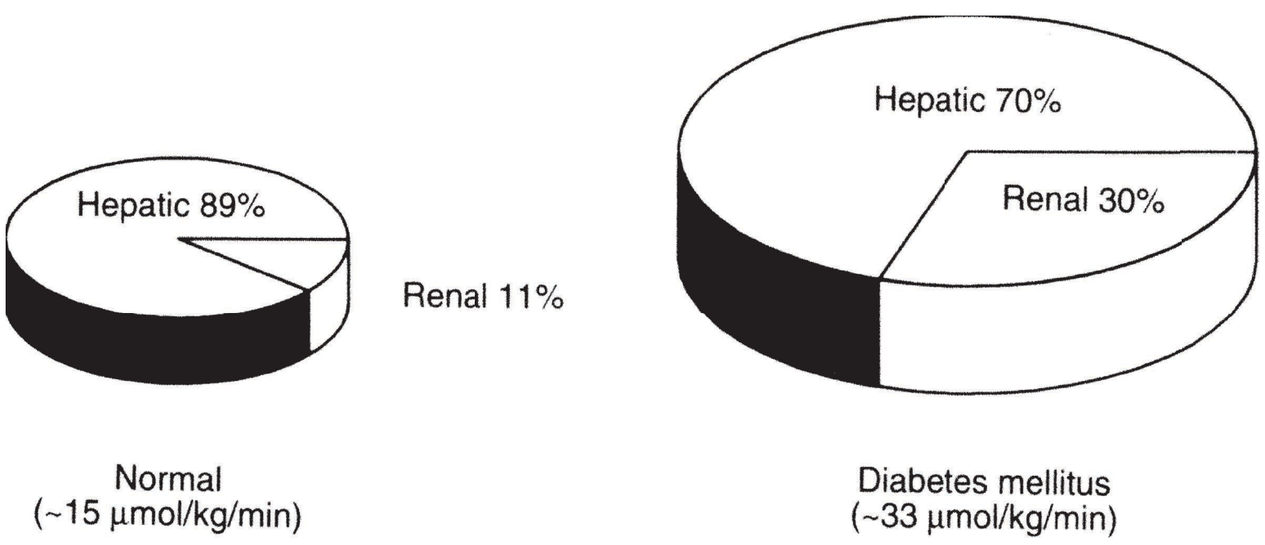

FIGURE 74.2 Contributions of the liver and the kidney to endogenous glucose production in conscious normal and diabetic dogs. Total glucose production is indicated in parentheses. (From Adrogué HJ. Glucose homeostasis and the kidney. *Kidney Int.* 1992;42:266.)

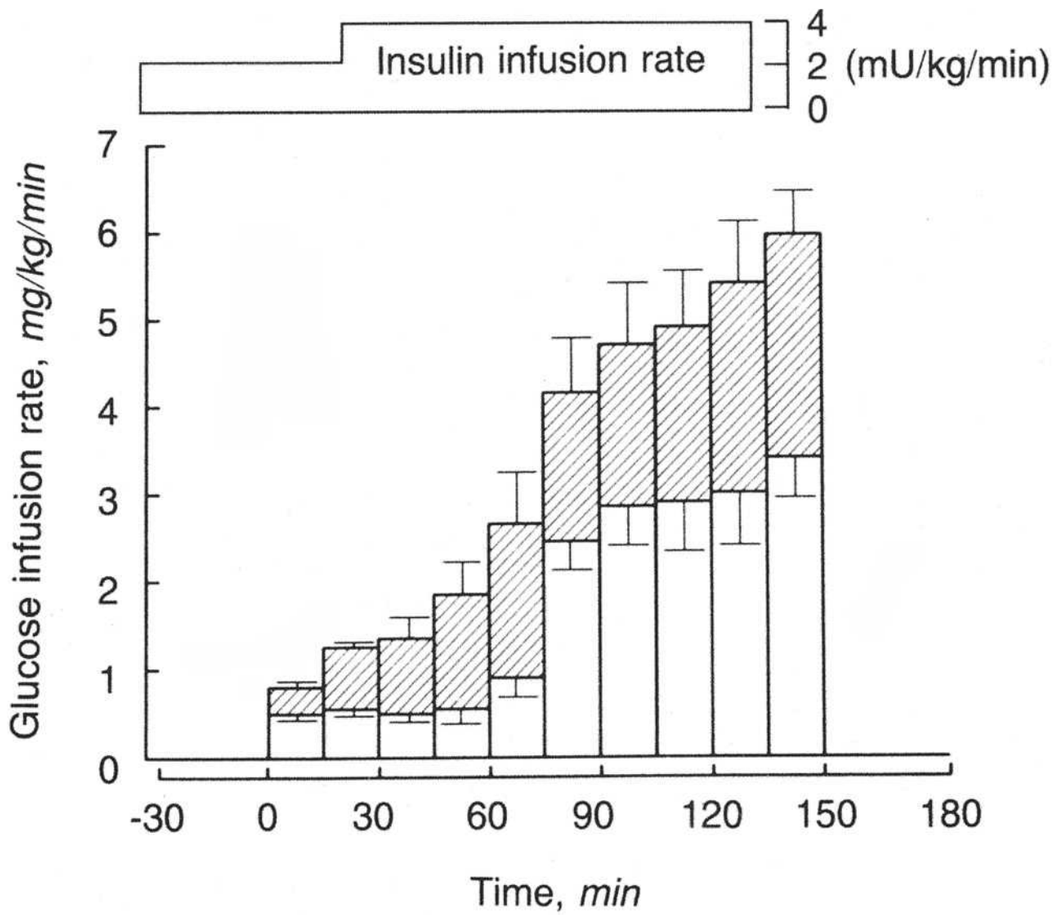

FIGURE 74.3 Rate of glucose infusion required to maintain euglycemia during insulin infusion studies in normal and acidemic dogs (respiratory acidosis, arterial pH = 7.18). Open area in each column represents the value in acidemic dogs; the entire column is the value in normal dogs. (From Adrogué HJ. Glucose homeostasis and the kidney. *Kidney Int*. 1992;42:1266.)

Because the total of the Na^+ and K^+ concentrations in the urine falls short of that in serum, osmotic diuresis elevates serum [Na^+] and [Cl^-]; moderation of hyponatremia or frank hypernatremia can ensue.[23,27] However, other factors also act to modify the serum [Na^+] and [Cl^-].[27] Some Na^+ enters cells replacing cellular K^+ losses, thereby decreasing serum [Na^+]. Urinary losses of Na^+ as ketone salts tend to increase serum [Cl^-], whereas selective Cl^- depletion during vomiting tends to cause hypochloremia. Further, the intake of fluid and electrolytes (sodium, potassium, and chloride) influences serum [Na^+] and [Cl^-]. Differences in the magnitude of these phenomena from one patient to another account for the variability in serum electrolyte composition observed at presentation. Table 74.2 reviews the admitting laboratory values of patients with DKA.[8] Note that serum [Na^+] is usually depressed; the rare presence of hypernatremia is indicative of a profound water depletion, usually seen in the most critically ill patients.

Prerenal azotemia due to volume depletion is almost always present in uncontrolled diabetes and is usually reversible, but occasionally it can progress to acute tubular necrosis.[28,29] The levels of plasma urea nitrogen, creatinine, total protein, uric acid, hematocrit, and hemoglobin can all be elevated on admission for DKA, a reflection of ECF contraction, and/or renal dysfunction, but they normalize swiftly after volume repletion.

Hyperlipidemia

Diabetes mellitus is commonly associated with hyperlipidemia, which in turn may reduce measured serum sodium concentration, causing the so-called pseudohyponatremia or false hyponatremia. This electrolyte disorder is characterized by a normal [Na^+] in plasma water despite a diminished [Na^+] in a plasma or serum sample. The decreased [Na^+] arises from an increased solid phase of plasma owing to severe hyperlipidemia or hyperproteinemia (e.g., myeloma). If [Na^+] is measured directly (without dilution of the sample) with ion-sensitive electrodes instead of flame photometry (the latter being the classic method), a normal value will be found; thus, this type of hyponatremia is false because: (1) the [Na^+] in plasma water is normal, and (2) its detection is dependent on the method used for measurement of [Na^+]. Pseudohyponatremia does not produce, of course, any of the symptoms associated with hypotonic hyponatremia. Furthermore, measured plasma osmolality is normal in pseudohyponatremia, because the solute concentration in plasma water is not altered.[23]

Let us compare the hyponatremia owing to hyperglycemia or hypertonic infusions (e.g., mannitol) with that caused by hyperlipidemia. The decreased [Na^+] owing to hyperglycemia or hypertonic infusions is not a form of pseudohyponatremia because [Na^+] in plasma water also is diminished. The ECF accumulation of solutes of relatively small molecular size, observed with hyperglycemia or hypertonic infusions, increases extracellular tonicity, which in turn osmotically pulls water from the intracellular fluid (ICF), diluting the [Na^+] in ECF. By contrast, high plasma levels of large-molecular-size solutes (e.g., hypertriglyceridemia) fail to alter extracellular tonicity and, therefore, do not cause a shift of water from the ICF to the ECF. Thus, pseudohyponatremia is a spurious form of isoosmolar and isotonic hyponatremia identified when severe hyperlipidemia or paraproteinemia increases substantially the solid phase of plasma and the [Na^+] is measured by means of flame photometry. The increasing availability of direct measurement of serum sodium with ion-specific electrodes has all but eliminated this laboratory artifact.[23]

Defect in Water Homeostasis

Examination of the defect in water homeostasis that accompanies diabetes mellitus requires a brief overview of this topic.[23–25] The disorders of salt and water balance may be classified into three major categories: (1) abnormalities in the size of body fluid compartments, (2) disturbances in the tonicity of body fluids, and (3) a selective deficit or excess of chloride with respect to sodium.[25] The first group of disorders comprises an enlargement ("volume expansion") and a reduction ("volume depletion or contraction") in the size of the ECF compartment, which are produced by a combined salt and water excess and a combined salt and water deficit, respectively. Disturbances in the tonicity of body fluids include increases (e.g., hypernatremia) and decreases (e.g., hypotonic hyponatremia) in the effective osmolality of body fluids. In contrast to the first group in which salt and water excess or deficit develops with normal proportionality, a discordant abnormality in salt and water balance occurs in disorders of body fluid tonicity. The third group of salt and

74.2 Salient Laboratory Abnormalities on Admission for Diabetic Ketoacidosis

Parameter	Value			Comments
Glucose	250 to 750 mg/dL			Values below 200 mg/dL ("euglycemic DKA") can be seen, especially in alcoholics or pregnant insulin-dependent diabetics; also, values above 1,000 mg/dL can be seen, especially in severe volume contraction leading to renal failure and interruption of glucosuria; glucose concentration not related to severity of DKA
Serum ketones	Positive in plasma diluted 1:1 or greater			Nitroprusside reagent (Ketostix, Acetest) does not react with β-hydroxybutyrate; color reaction is mostly (>80%) due to acetoacetate
Bicarbonate	<18 mmol/L			Always reduced in DKA unless complicated by coexisting metabolic alkalosis
pH	<7.30			Always reduced in DKA unless complicated by coexisting metabolic alkalosis or respiratory alkalosis
	Plasma Concentration			
	Low	**Normal**	**High**[a]	
Sodium	67	26	7	Body stores depleted (7–10 mEq/kg)
Chloride	33	45	22	
Potassium	18	43	39	Body stores depleted (3–5 mEq/kg)
Magnesium	7	25	68	
Phosphate	11	18	71	Body stores depleted (5–7 mEq/kg)
Calcium	28	68	4	
BUN, creatinine	High			Because creatinine can be spuriously elevated (cross-reaction with acetoacetate), BUN can better reflect renal function
White blood cell count	Usually high			Not necessarily indicative of infection; associated with lymphopenia and eosinopenia
Hemoglobin, hemacri, total protein	Frequently increased			Due to intravascular volume depletion
SGOT, SGPT, LDH, CPK	High, 20% to 65%			Partially due to interference of acetoacetate with colorimetric assays; elevated CPK might be related to phosphate depletion and possible associated rhabdomyolysis
Amylase	Often increased			Isoenzyme evaluation reveals that site of origin is pancreas (50%), salivary (36%), or mixed (14%)

[a]Modified from Kreisberg RA. Diabetic ketoacidosis: new concepts and trends in pathogenesis and treatment. Ann Intern Med. 1978;88:681.
DKA, diabetic ketacidosis; BUN, blood urea nitrogen; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase.

water disorders is characterized by an abnormal relationship between the $[Na^+]_p$ and $[Cl^-]_p$ (plasma concentration). Although the $[Na^+]_p$ is generally maintained within normal limits in these disorders because it is dependent on overall water homeostasis, the $[Cl^-]_p$ is either abnormally low or high. The major representatives of a selective deficit or excess of chloride with respect to sodium are hypochloremic metabolic alkalosis and hyperchloremic metabolic acidosis, respectively. These acid–base disorders are reviewed in the section dealing with such abnormalities.

Disturbances in salt balance are the primary causes of volume excess and depletion, whereas disorders in water balance are responsible for the development of the tonicity disorders, hypertonicity (hypernatremia), and hypotonicity (hyponatremia). Because sodium chloride (NaCl) excess only transiently increases tonicity, leading to augmented antidiuretic hormone (ADH) (i.e., arginine vasopressin) secretion and secondary water retention, hypernatremia is not clinically observed. Expansion of the ECF volume, instead, is the hallmark of a primary NaCl excess. In a comparable fashion, NaCl deficit only transiently decreases tonicity, inhibiting ADH secretion with secondary increase in water excretion, so that hyponatremia is not observed, whereas volume depletion becomes the major manifestation of this electrolyte imbalance. A primary and exclusive disturbance in water balance, deficit and excess, causes hypertonicity (hypernatremia) and hypotonicity (hyponatremia), respectively, but does not produce a major alteration in the size of the fluid compartments because the latter is primarily determined by the osmolar content in each compartment, and the change in water content is distributed throughout the body fluids.[25]

Dysnatremias in Diabetes Mellitus. A defect in water homeostasis in patients with diabetes mellitus might lead to either hypotonic hyponatremia or hypernatremia in response to positive or negative water balance, respectively.[25] Water and electrolyte losses caused by vomiting or diarrhea are commonly encountered in uncontrolled diabetes as well as patients with diabetes experiencing target organ damage in the alimentary tract (e.g., gastroparesis, nocturnal diarrhea). In addition, excessive urinary fluid losses may develop as a result of osmotic diuresis, use of diuretics, adrenal insufficiency, or other causes. Whether hypotonic hyponatremia or hypernatremia develops is dependent on the concomitant water intake. Hypernatremia might be observed if water intake is insufficient, whereas a large salt-free fluid intake might lead to hyponatremia. Long-standing diabetes mellitus commonly predisposes or leads to heart failure, renal failure, or both, thereby impairing renal water excretion that may lead to hypotonic hyponatremia. Concomitant medication, including diuretics, might also play a role in the development of hyponatremia.

Abnormal $[Na^+]_p$ can produce signs and symptoms owing to central nervous system dysfunction and the clinical manifestations elicited by opposite changes in tonicity are remarkably similar, except for seizures that are mostly caused by cerebral edema secondary to dilutional (hypotonic) hyponatremia. When the patient's osmoregulating mechanisms (thirst, changes in water intake and ADH levels, renal water retention or excretion) fail, an increase or decrease in plasma tonicity and $[Na^+]_p$ develops. Plasma hypertonicity induces brain water loss, whereas hypotonicity produces water gain in this organ, accompanied in both cases by parallel volume changes. As a defense mechanism to correct brain volume changes, the intracellular osmolytes of this organ increase in hypernatremia and decrease in hypotonic hyponatremia. The adaptive increase in brain osmolytes reflects a modest increase in cellular K^+ and accumulation of organic solutes (e.g., glutamine, glutamate, and other organic metabolites), which are referred to as idiogenic osmoles. Conversely, the adaptive decrease in brain osmolytes reflects a decrease in cellular K^+ accompanied by a diminished concentration of idiogenic osmoles. These secondary responses of the brain to altered extracellular tonicity can be demonstrated within a few hours of the initiation of abnormal tonicity and are complete within a few days.

Hypotonic or Dilutional Hyponatremia. It represents an excess of water in relation to existing sodium stores, which can be decreased, essentially normal, or increased. Retention of water most commonly reflects the presence of conditions that impair renal excretion of water; in a minority of cases, however, it is caused by excessive water intake, with a normal or nearly normal excretory capacity.

Conditions of impaired renal excretion of water are categorized according to the characteristics of the ECF volume, as determined by clinical assessment. Decreased ECF volume can result from renal sodium loss (e.g., glucosuria-induced osmotic diuresis) or extrarenal sodium loss (e.g., vomiting). Conditions with essentially normal ECF volume include thiazide diuretics, syndrome of inappropriate secretion of antidiuretic hormone, decreased intake of solutes, hypothyroidism, and glucocorticoid insufficiency. Increased ECF volume with hyponatremia can be observed in pregnancy, renal failure, congestive heart failure, cirrhosis, and nephrotic syndrome. With the exception of renal failure, these conditions are characterized by high plasma concentrations of ADH despite the presence of hypotonicity; arterial underfilling induces baroreceptor-mediated nonosmotic release of ADH that overrides the osmotic regulation of the hormone, thereby impairing urinary dilution and causing hyponatremia. Depletion of potassium accompanies many of these disorders and contributes to hyponatremia because the sodium concentration is determined by the ratio of the "exchangeable" (i.e., osmotically active) portions of the body's sodium and potassium content to total body water. Patients with hyponatremia induced by thiazides can present with variable hypovolemia or apparent euvolemia, depending on the magnitude of the sodium loss and water retention.

Excessive water intake can cause hyponatremia by overwhelming normal water excretory capacity (e.g., 15 to 20 L per day). Frequently, however, psychiatric patients with excessive water intake have plasma arginine vasopressin concentrations that are not fully suppressed and urine that is not maximally dilute, thus contributing to water retention.

The optimal treatment of hypotonic hyponatremia requires balancing the risks of hypotonicity against those of therapy.[23] The presence of symptoms and their severity largely determine the pace of correction. Patients with symptomatic hyponatremia and dilute urine (osmolality, <200 mOsm per kg water) but with less serious symptoms usually require only water restriction and close observation. Severe symptoms (e.g., seizures or coma) call for infusion of hypertonic saline. On the other hand, patients who have symptomatic hyponatremia with concentrated urine (osmolality ≥200 mOsm per kg water) in association with a hypovolemic state are best treated with isotonic saline; those having clinical euvolemia or hypervolemia require infusion of hypertonic saline.

There is no consensus about the optimal treatment of symptomatic hyponatremia.[23] Nevertheless, correction should be of a sufficient pace and magnitude to reverse the manifestations of hypotonicity but not be so rapid and large as to pose a risk of the development of central pontine myelinolysis. Osmotic demyelination is a serious disorder and can develop one to several days after aggressive treatment of hyponatremia by any method, including water restriction alone. Shrinkage of the brain triggers demyelination of pontine and extrapontine neurons that can cause neurologic dysfunction, including quadriplegia, pseudobulbar palsy, seizures, coma, and even death. Hepatic failure, potassium depletion, and malnutrition increase the risk of the complication. Physiologic considerations indicate that a relatively small increase in the serum $[Na^+]$, on the order of 5%, should substantially reduce cerebral edema in patients with symptomatic hypotonic hyponatremia. Even seizures induced by hyponatremia can be stopped by rapid increases in the serum $[Na^+]$ that average only 3 to 7 mEq per L. Most reported cases of osmotic demyelination occurred after rates of correction that exceeded 12 mEq per L per day were used, but isolated cases occurred after corrections of only 9 to 10 mEq per L in 24 hours or 19 mEq per L in 48 hours. After weighing the available evidence and the all-too-real risk of overshooting the mark, we recommend a targeted rate of correction that does not exceed 8 mEq per L on any day of treatment. Remaining within this target, the initial rate of correction can still be 1 to 2 mEq per L per hour for several hours in patients with severe symptoms.

The rate of infusion of the selected solution can be derived expediently by applying the following equations:

$$\Delta[Na^+]_s = \frac{[Na^+]_{inf} - [Na^+]_s}{TBW + 1} \quad (74.1)$$

Equation 74.1 projects the impact of 1 L of any infusate on the patient's $[Na^+]_s$

$$\Delta[Na^+]_s = \frac{[Na^+ + K^+]_{inf} - [Na^+]_s}{TBW + 1} \quad (74.2)$$

Equation 74.2 is a simple derivative of equation 74.1 and projects the impact of 1 L of any infusate containing sodium and potassium on the patient's $[Na^+]_s$

The preceding equations project the change in serum $[Na^+]$ elicited by the retention of 1 L of any infusate.[30] Dividing the change in serum sodium targeted for a given treatment period by the output of this equation determines the volume of infusate required, and hence the rate of infusion. Although water restriction ameliorates all forms of hyponatremia, as explained, it is not the optimal therapy in all cases.

Corrective measures for nonhypotonic hyponatremia are directed at the underlying disorder rather than at the hyponatremia itself. Administration of insulin is the basis of treatment for uncontrolled diabetes, but deficits of water, sodium, and potassium also should be corrected.

Hypernatremia. Defined as a rise in the $[Na^+]_p$ to a value exceeding 145 mEq per L, it represents a deficit of water in relation to the body's sodium stores, which can result from a net water loss or a hypertonic sodium gain.[24] Net water loss accounts for the majority of cases of hypernatremia. It can occur in the absence of a sodium deficit (pure water loss) or in its presence (hypotonic fluid loss). Net water loss can result from pure water (e.g., hypodipsia, diabetes insipidus) or hypotonic fluid loss, the latter secondary to renal, gastrointestinal, or cutaneous causes.

An equation[31] that allows projection of the expected $\Delta[Na^+]_s$ in response to losing 1 L of fluid (fl) of variable electrolyte content from the renal or extrarenal route is as follows:

$$\Delta[Na^+]_s = \frac{[Na^+]_s - [Na^+ + K^+]_{fl}}{TBW - 1} \quad (74.3)$$

Multiplying the output of the equation by the volume of the fluid loss in liters provides a quantitative estimate of the impact of the fluid loss on $[Na^+]_s$. Obviously, application of this equation has greater practical value in the presence of large fluid losses (e.g., large gastrointestinal drainage, polyuria).

Hypertonic sodium gain usually results from clinical interventions (e.g., sodium bicarbonate infusion, hypertonic enemas) or accidental sodium loading. Signs and symptoms of hypernatremia largely reflect central nervous system dysfunction and are prominent when the increase in the serum $[Na^+]$ is large or occurs rapidly (i.e., over a period of hours). Most outpatients with hypernatremia are either very young or very old. Common symptoms in infants include hyperpnea, muscle weakness, restlessness, a characteristic high-pitched cry, insomnia, lethargy, and even coma. Convulsions are typically absent except in cases of inadvertent sodium loading or aggressive rehydration. Brain shrinkage induced by hypernatremia can cause vascular rupture, with cerebral

bleeding, subarachnoid hemorrhage, and permanent neurologic damage or death. Brain shrinkage is countered by an adaptive response that is initiated promptly and consists of solute gain by the brain that tends to restore lost water.

Proper treatment of hypernatremia requires a two-pronged approach: addressing the underlying cause and correcting the prevailing hypertonicity.[24] Managing the underlying cause may mean stopping gastrointestinal fluid losses; controlling pyrexia, hyperglycemia, and glucosuria; withholding lactulose and diuretics; treating hypercalcemia and hypokalemia; moderating lithium-induced polyuria; or correcting the feeding preparation. In patients with hypernatremia that has developed over a period of hours (e.g., those with accidental sodium loading) rapid correction improves the prognosis without increasing the risk of cerebral edema, because accumulated electrolytes are rapidly extruded from brain cells. In such patients reducing the $[Na^+]_p$ by 1 mEq/L/hour is appropriate. A slower pace of correction is prudent in patients with hypernatremia of longer or unknown duration, because the full dissipation of accumulated brain solutes occurs over a period of several days. In such patients, reducing the $[Na^+]_p$ at a maximal rate of 0.5 mEq/L/hour prevents cerebral edema and convulsions. Consequently, we recommend a targeted fall in the $[Na^+]_p$ of 10 mEq/L/day for all patients with hypernatremia except those in whom the disorder has developed over a period of hours. The goal of treatment is to reduce the $[Na^+]_p$ to 145 mEq per L. Because ongoing losses of hypotonic fluids, whether obligatory or incidental, aggravate the hypernatremia, allowance for these losses must also be made.

The preferred route for administering fluids is the oral route or a feeding tube; if neither is feasible, fluids should be given intravenously. Only hypotonic fluids are appropriate, including pure water, 5% dextrose, 0.2% NaCl (referred to as one quarter isotonic saline), and 0.45% NaCl (one half isotonic saline). The more hypotonic the infusate, the lower the infusion rate required. The volume should be restricted to that required to correct hypertonicity because the risk of cerebral edema increases with the volume of the infusate. Except in cases of frank circulatory compromise, 0.9% NaCl (isotonic saline) is unsuitable for managing hypernatremia.

After selecting the appropriate infusate, the physician must determine the rate of infusion. This can be easily calculated with the use of equations 74.1 and 74.2 which estimate the change in the serum sodium concentration caused by the retention of 1 L of any infusate. The sole indication for administering isotonic saline to a patient with hypernatremia is a depletion of ECF volume sufficient to cause substantial hemodynamic compromise. Even in this case, after a limited amount of isotonic saline has been administered to stabilize the patient's circulatory status, a hypotonic fluid (i.e., 0.2% or 0.45% NaCl) should be substituted in order to restore normal hemodynamic values while correcting the hypernatremia. If a hypotonic fluid is not substituted for isotonic saline, the ECF volume may become seriously overloaded.

Defect in Sodium Homeostasis

The quantity of solutes in each of the main fluid compartments determines its size, so that deficit or excess of solutes in a particular space will shrink or swell that space in comparison with the other compartments.[25] The partition of water is determined by the osmotic activity of the solutes confined to each body compartment. One major solute is responsible for the size of each fluid compartment. These solutes are potassium, sodium, and proteins, for the intracellular, extracellular, and intravascular spaces, respectively. Because the hydraulic permeability of most cell membranes is very high, solute-free water freely and rapidly moves across all body compartments.

Body stores of NaCl are determined by the balance of its intake and excretion. Under normal circumstances, NaCl intake is derived from the diet and its excretion occurs by urinary loss. A positive NaCl balance (intake exceeds excretion) increases salt stores, whereas a negative one (excretion exceeds intake) decreases salt stores. The effect of increased NaCl stores is expansion of ECF volume, whereas decreased NaCl stores lead to a reduced ECF volume. Thus, an NaCl deficit in body fluids (e.g., vomiting, diarrhea) reduces ECF volume, including the intravascular compartment. By contrast, NaCl excess (e.g., congestive heart failure) expands ECF volume and can produce overt peripheral edema and accumulation of fluid in major body cavities (pleural effusion, ascites). A major decrease in serum protein concentration (mostly albumin) diminishes intravascular volume and promotes expansion of the interstitial compartment (e.g., nephrotic syndrome, hepatic cirrhosis). Diabetes mellitus is a common cause of both volume depletion and volume expansion. The former disturbance is characteristically observed in the course of severe metabolic complications of this disease, namely, DKA and NKH. Conversely, volume expansion is observed in patients having chronic diabetic complications, including congestive heart failure, nephrotic syndrome, and renal failure.

Volume Depletion. Volume depletion in diabetic patients can result from fluid loss (e.g., renal and/or extrarenal) or from fluid sequestered into a "third space" (e.g., acute pancreatitis). Renal losses may occur in the presence of normal intrinsic renal function (e.g., osmotic diuresis caused by glucosuria or urea diuresis, adrenal insufficiency, diuretics) or in acute and chronic renal disease (e.g., acute tubular necrosis, diabetic glomerulosclerosis). Osmotic diuresis owing to renal excretion of glucose can produce a large natriuresis, leading to volume depletion. Patients with significant hyperglycemia, including those with DKA or nonketotic coma, may have a fluid deficit of 10% or more of body weight. Extrarenal losses include those from the gastrointestinal tract (e.g., vomiting, diarrhea, gastrointestinal suction, fistulas) and those from the skin (sweat, burns, extensive

skin lesions). Fluid sequestration into a third space occurs with abdominal accumulation (e.g., intestinal obstruction, pancreatitis, peritonitis), bleeding, skeletal fractures, and obstruction of a major venous system.

The patient's history, physical examination, and laboratory data are critical elements in the evaluation of volume depletion, allowing the physician to (1) assess the severity of the deficit, and (2) establish its cause. Immediate recognition of hypovolemic shock is of utmost importance, because rapid intravascular volume expansion might prevent tissue injury and death. Evaluation of its severity allows establishment of the rate of infusion and the total fluid requirements. Recognition of the factors responsible for fluid loss permits initiation of specific therapeutic measures to correct the volume depletion.[25]

Patients with volume depletion have signs and symptoms related to (1) the process responsible for volume depletion, and (2) the hemodynamic consequences of fluid loss. Through the first group of manifestations it is possible to recognize the cause of volume depletion, such as loss or sequestration of fluid. The second group of signs and symptoms includes hypotension, decreased cardiac output, and tachycardia owing to intravascular volume depletion. In addition, diminished tissue perfusion produces altered mental status, generalized weakness, and occasionally severe organ damage (e.g., acute tubular necrosis, cerebral ischemia, myocardial infarction).

The severity of volume deficit may be estimated through evaluation of blood pressure, heart rate, neck veins and venous pressure, skin turgor, moistness of mucous membranes, changes in body weight, and blood and urine indices. If volume depletion results from mechanisms other than hemorrhage, the fluid loss produces hemoconcentration with increased hematocrit (Hct). The ECF volume deficit can be estimated in states of a primary extravascular fluid loss from the rise in Hct as follows:

$$\text{ECV volume deficit} = 0.25 \times \text{body weight (kg)} \times (\text{actual Hct/normal Hct} - 1) \quad (74.4)$$

where 0.25 represents the fraction of ECF per kg of body weight (250 mL per kg). Because the normal range of Hct is relatively wide (38% to 45%), the patient's baseline Hct usually is unknown, and blood loss may have occurred, the reliability of changes in Hct is only modest. Therefore, a precise estimation of volume deficit is difficult. The loss of body weight from its baseline level (body weight prior to the episode of volume depletion) is a clinically useful index to estimate volume deficit, as follows:

$$\Delta \text{ body weight (kg)} = \text{fluid deficit (L)} \quad (74.5)$$

The change in body weight is unreliable for the estimation of fluid deficit in patients with "third space" sequestration. If $[Na^+]_p$ remains within normal limits, the weight loss in kilogram truly represents loss of isotonic fluid. Volume deficit accompanied by hypernatremia or hyponatremia indicates the existence of a disproportionate water loss compared to Na^+ loss.

Pertinent blood indices that are most useful in the diagnosis and management of volume depletion include: (1) blood urea nitrogen (BUN) and serum creatinine levels; (2) Hct, total plasma protein, and/or albumin values; and (3) levels of serum electrolytes, including Na^+, K^+, Cl^-, and total carbon dioxide (almost identical to plasma $[HCO_3^-]$). In volume depletion, BUN and plasma creatinine increase because of an overall depression of renal function, manifested by oliguria, and reduced glomerular filtration rate (GFR) and renal plasma flow. Increased plasma creatinine is caused by a reduced GFR (when muscle necrosis, which could release this substance into the circulation, is absent). Conversely, an elevated BUN, not accompanied by increased plasma creatinine and reduced GFR, reflects enhanced renal reabsorption of urea accompanied by increased salt and water reabsorption. Consequently, the ratio of BUN over plasma creatinine increases from its normal value of 10:1 to 15:1 or more. Hematocrit and concentration of plasma proteins also can increase in volume depletion, a process referred to as hemoconcentration. Alterations in serum electrolytes are commonly observed and they depend on the composition of the fluid lost (e.g., vomiting produces hypokalemia and metabolic alkalosis) as well as the concomitant water and electrolyte intake.

With respect to fluid therapy in volume depletion, considering that oral intake is the physiologic pathway for the entry of fluids, this route should be always considered. Oral replacement therapy is effective, relatively inexpensive, and noninvasive; does not require hospitalization; and saves several million patients (mostly children in developing nations) each year from death. Nevertheless, the presence of vomiting, ileus, or altered mental status precludes its use, mandating intravenous administration of fluid. Most frequently, however, volume repletion in hospitalized patients is performed by the parenteral (intravenous) route.

Volume repletion should be promptly secured because severe volume depletion frequently produces a major reduction in intravascular volume and hypovolemic shock. The type of fluid to be used depends on the cause of volume depletion. Hypovolemia caused by bleeding (e.g., peptic ulcer, rupture of aortic aneurysm) must be treated with blood products or plasma volume expanders (e.g., packed red cells, albumin, or dextran solutions), whereas that resulting from renal or extrarenal losses and fluid sequestration in body cavities (e.g., ileus, ascites) must be treated with saline, dextrose in saline, or Ringer's solution. Plasma volume expanders can be used in the initial phase of treatment to secure a more rapid restoration of hemodynamic status in all patients with shock.

Various intravenous solutions can be selected in fluid therapy.[25] The most commonly used intravenous fluids consist of a NaCl-containing solution (NaCl 0.23%, 0.45%, and 0.9%, known as ¼ normal saline, ½ normal saline, and

normal saline, respectively) with or without 5% dextrose. The term normal used in reference to intravenous solutions does not imply "normality" (chemical notation) but simply refers to the isotonicity of intravenous solutions with respect to body fluids. It is more proper to refer to these solutions as ¼ isotonic saline, ½ isotonic saline, and isotonic saline. Although 5% dextrose in water is isotonic with body fluids, the glucose is metabolized so that this solution provides solute-free water without effective long-lasting osmoles (yet providing some caloric intake). The NaCl added to intravenous solutions provides effective osmoles that are preferentially retained in ECF. The efficacy of the various solutions with respect to volume deficit correction is a function of their NaCl concentration, with normal saline as the most effective one and dextrose in water without NaCl the least effective. The selection of intravenous solution is also determined by the patient's $[Na^+]_p$; hypernatremic patients are most frequently treated with NaCl-free solutions (e.g., 5% dextrose in water), whereas those with hyponatremia are usually given isotonic saline or hypertonic (e.g., NaCl 3.0%) saline solutions. It is important to realize the expected changes in the volume of ECF and ICF in response to various solutions. The infusion of normal saline expands the ECF exclusively (ECF volume increment is identical to the volume infused); thus, ICF volume remains unaltered. The infusion of ½ isotonic saline expands both the ECF and ICF, with the former receiving 73% and the latter 27% of the volume load. Finally, a salt-free water infusion (e.g., 5% dextrose in water) will also expand both the ECF and ICF, but in this case, the latter receives 60% of the volume load. In summary, a pure water infusion expands all body compartments but predominantly the ICF, whereas isotonic saline expands the ECF exclusively.[23]

Because patients in hypovolemic shock are at immediate risk of death or ischemic tissue injury, the initial fluid infusion should be at the maximal flow allowed by the intravenous catheter ("wide open"); once blood pressure and tissue perfusion return to acceptable levels, the rate must be diminished to approximately 100 mL per hour to minimize the risk of pulmonary edema, owing to rapid intravascular expansion. Patients with acceptable hemodynamic parameters should receive fluid at initial rates of 100 to 200 mL per hour, with subsequent reduction after 6 to 12 hours to rates of about 100 mL per hour, to secure gradual repletion of all fluid compartments without imposing undue stress on the circulation. Exceptions to these rules are patients with extreme volume depletion (e.g., DKA, NKH) or large ongoing fluid losses (e.g., continuous drainage of large volume of gastrointestinal secretions, postobstructive diuresis, and diabetes insipidus) who might require fluids at a higher rate of infusion as described in the corresponding section of this chapter.

Proper monitoring of fluid replacement therapy is accomplished by evaluation of arterial blood pressure, presence of collapsed or distended neck veins, and urine output to establish the optimum rate of fluid replacement. Additional information might be necessary in critically ill patients, including monitoring of left- and right-sided heart filling pressures, blood pressure measurement through an intra-arterial line, arterial and/or venous blood gas analysis, and sequential chest X-ray films to detect pulmonary venous congestion and interstitial edema.

Volume Expansion. A syndrome of volume expansion caused by overt salt and water retention is commonly observed in long-standing diabetes mellitus.[32,33] Both forms of generalized edema, the so-called primary as well as the secondary types, are encountered. In primary edema, renal retention of salt and water is the initial event that leads to expansion of ECF volume (e.g., diabetic glomerulosclerosis with reduced GFR and avid tubular reabsorption of salt and water). In secondary edema, also called underfill edema, the presence of renal hypoperfusion, owing to decreased "effective arterial circulating blood volume," initiates salt and water retention by the kidney (e.g., diabetes mellitus with congestive heart failure). Thus, the kidney is always involved in the development of positive salt and water balance that leads to generalized edema.[25] It must be recognized that salt and water retention, owing to primary renal disease and congestive heart failure, is the main cause of generalized edema and normal or near-normal serum albumin. Absence of proteinuria argues against renal disease as the primary cause of fluid retention. Patients with heart failure usually have either minimal or mild urinary protein excretion (1+ or 2+ on dipstick determination), whereas those with nephrotic syndrome have, as a rule, severe proteinuria (4+ dipstick). The fluid retention observed in nephrotic syndrome appears to occur as a combination of primary and secondary edema.

The management of localized and generalized edema must be directed, if possible, at the primary cause of fluid accumulation. Effective treatment of the primary cause leads to resolution of the edema. Therapy of the primary process in congestive heart failure can involve the use of afterload-reducing agents, digoxin, and diuretics. Patients with generalized edema most frequently require treatment of the fluid overload in addition to that directed at the primary disease. Correction of fluid overload involves restriction of dietary NaCl, and if this is unsuccessful, the use of diuretic therapy. In addition, both localized and generalized edema are ameliorated by bed rest and elevation of the edematous body area. The management of generalized edema caused by congestive heart failure, nephrotic syndrome, and diabetic glomerulosclerosis is examined in detail in other chapters.

Defect in Potassium Homeostasis

The levels of total body K^+ stores are established by the external K^+ balance, which in turn is determined by the difference between K^+ intake and excretion. The internal K^+ balance refers to the control mechanisms for the distribution of total body K^+ stores between the ICF and the ECF. The major factors that alter internal K^+ balance include hormones (insulin, catecholamines), the acidity of body fluids,

the levels of other electrolytes, the tonicity of body fluids, and drugs.[34]

Insulin is a major modulator of extrarenal K^+ homeostasis and promotes K^+ uptake in many cell types, including those from skeletal muscle and liver. The hypokalemic action occurs at very low concentrations of insulin and is independent of the effect of insulin on glucose uptake. The precise mechanism of this action remains to be fully defined but appears to involve the activation of several transport proteins, including stimulation of the Na^+-K^+-ATPase, stimulation of the Na^+-H^+ exchanger, and changes in ionic conductance of certain K^+ channels.[35] Direct stimulation of the Na^+-K^+ pump by insulin induces the translocation of K^+ into the cell interior (entry of two K^+ and exit of three Na^+). This action results in hyperpolarization of the membrane potential (a more negative cell interior). Such hyperpolarization of the cell membrane establishes a new electrical gradient, which favors cellular K^+ entry, and deactivates K^+ channels, which inhibits cellular K^+ exit. Thus, the secondary effects of insulin on the membrane potential increase the hypokalemic action of this hormone.

By stimulating the Na^+-H^+ exchanger, insulin promotes the cellular entry of Na^+ and the cellular exit of H^+. The entry of Na^+ increases the intracellular [Na^+], which further stimulates the Na^+-K^+-ATPase. The cellular exit of H^+ results in cytosolic alkalinization, which in turn increases the K^+-binding capacity for intracellular anions and stimulates the Na^+-K^+ pump, therefore favoring cellular K^+ loading.

A third mechanism for the hypokalemic effect of insulin is mediated from its action on K^+ channels. Insulin controls gating of the inward rectifier K^+ channel of skeletal muscle. This channel is responsible for most of the K^+ conductance of the skeletal muscle in the resting state. It allows K^+ to flow into cells much more easily than it exits from them. Consequently, when the cell membrane is hyperpolarized, the high inward conductance facilitates cellular K^+ entry, whereas when the cell membrane is depolarized, the low outward conductance reduces K^+ exit from cells. Insulin exaggerates the inward rectifying properties of this class of K^+ channel by a dual effect of stimulation of K^+ entry and depression of K^+ exit.

Glucagon also has significant effects on internal K^+ balance and plasma potassium levels.[36] Glucagon induces glycogen breakdown in the hepatocytes, releasing glucose and K^+; therefore, high glucagon levels can elicit a transient increase in $[K^+]_p$. An increase in plasma glucagon in acute metabolic acidosis has been described and this hormonal response might play a role in acidosis-induced hyperkalemia.[35]

K^+ Depletion with Hyperkalemia. The development of uncontrolled diabetes, including DKA, is usually accompanied by varying degrees of total body potassium depletion, which results from multiple causes, including massive kaliuresis secondary to glucosuria, decreased intake, and frequent vomiting. However, plasma potassium levels are rarely low at the time of hospitalization, ranging in most instances from normal to high levels and occasionally attaining dangerously elevated values. This paradoxical relationship has been classically attributed to the concomitant changes in blood acidity that would affect a shift of potassium out of the cells in exchange for hydrogen ions moving intracellularly.[37] However, several of the metabolic derangements observed in patients presenting with DKA are known to alter potassium metabolism and may contribute to the development of hyperkalemia. Endogenous ketoacidemia and hyperglycemia correlate with increased plasma potassium concentration on admission in patients with DKA.[36] However, exogenous ketoacidemia and hyperglycemia in the otherwise normal experimental animal fails to increase plasma potassium levels,[38,39] suggesting that the insulin deficit per se is the major cause of the hyperkalemia that develops in DKA.[36]

Serum pH and bicarbonate levels are known to alter plasma potassium levels. Whereas some studies indicated that the changes in plasma potassium concentration observed during acute acid–base disorders are consequent to the attendant changes in plasma pH, others showed that a low plasma bicarbonate concentration, under isohydric conditions, may induce hyperkalemia.[40,41] Increased effective serum osmolality is another abnormality characteristic of DKA that may affect serum potassium; extracellular hypertonicity resulting from the infusion of saline, mannitol, or glucose results in the translocation of potassium-rich cell water to the extracellular compartment.[42] Hyperglycemia of either endogenous or exogenous origin unaccompanied by ketoacidosis results in hyperkalemia in insulin-deficient diabetics, especially when hypoaldosteronism also is present.[39]

As previously described, glucagon may also play a role in the hyperkalemia of DKA. This hormone may cause an increased potassium output from the liver, an effect that is usually transient because of the counterregulatory enhancement of insulin secretion. However, in the presence of an impaired insulin secretion, as in patients with DKA, increments in plasma glucagon levels may result in uncontrolled hyperkalemia.[43]

An additional mechanism that may be involved in the deranged potassium homeostasis observed in diabetes mellitus is the sympathetic nervous system. Potassium tolerance has been found to be markedly impaired in chemically sympathectomized animals, but is improved in animals given a simultaneous infusion of epinephrine.[44] The effects of the adrenergic agents on the internal potassium balance are mediated by their effect on the plasma levels of insulin and glucagon, and a direct cellular effect on K^+ transport. Therefore, any physiologic condition or pharmacologic maneuver that blocks the β-adrenergic system could result in hyperkalemia, particularly during states of increased potassium load. Diabetic patients may have a suboptimal epinephrine response or altered peripheral sympathetic activity, resulting in potassium movement from the intracellular to

the extracellular space as well as an impairment in cellular entry of potassium.

K^+ Depletion with Hypokalemia. Hypokalemia can result from the redistribution or depletion of K^+ stores. The hypokalemia that results from redistribution is caused by cellular uptake of K^+ from the ECF; K^+ redistribution can occur simultaneously with K^+ depletion so that the two processes leading to hypokalemia can have additive effects. The hypokalemia observed with K^+ depletion is characterized by a reduction in the K^+ content of all body fluids.[34]

Potassium depletion can occur with diabetes mellitus when dietary K^+ intake is very low and therefore fails to counterbalance the obligatory urinary K^+ losses associated with glucosuria. However, if K^+ losses are abnormally high, potassium depletion might develop in association with a normal dietary K^+ intake. Potassium losses may be renal or extrarenal, but a combination of losses is commonly encountered. Total body K^+ deficit results in a greater absolute reduction of K^+ content in ICF than in ECF. Nevertheless, the percent deviation in K^+ content is considerably smaller in ICF than in ECF. In a similar fashion, the decrease in intracellular $[K^+]$ with K^+ depletion is significantly smaller than the decrease in $[K^+]_p$. With respect to the relationship between $[K^+]_p$ and the degree of K^+ deficit, a linear relationship with a slope of 0.3 mEq/L per 100 mEq of K^+ deficit $[\Delta[K^+]_p/\Delta K^+$ stores] has been described for patients with K^+ depletion in the absence of redistribution of K^+ stores. According to this relationship, a K^+ depletion of 10% of total body K^+ stores (350 mEq) produces a decrease in $[K^+]_p$ of approximately 1 mEq per L.

Diabetic gastroparesis is a common cause of vomiting leading to fluid and electrolyte losses. Protracted vomiting leads to hypokalemia that is largely caused by increased renal K^+ excretion. The increased kaliuresis is owing to HCO_3^- excretion consequent to HCl depletion (metabolic alkalosis) and to secondary hyperaldosteronism resulting from ECF volume depletion. The direct loss of K^+ as a result of vomiting is relatively small, considering that $[K^+]$ in gastric juice averages 15 mEq per L. Diuretic therapy for the management of accompanying hypertension and congestive heart failure is a common additional cause of potassium depletion. Within a week from the start of diuretic therapy, a mild decrease (0.3 to 0.6 mEq per L) in $[K^+]_p$ occurs, and this level remains constant thereafter unless an intercurrent illness that decreases K^+ intake (vomiting) or increases K^+ loss (diarrhea) develops. Hypokalemia is most commonly observed with thiazides (5% of patients) than with loop diuretics (1% of patients). The decrease in $[K^+]_p$ is directly proportional to the daily dosage and duration of action of the diuretic; thus, daily administration and high-dosage regimens of chlorthalidone, a long-acting thiazide, are more likely to produce severe K^+ depletion and hypokalemia. The antihypertensive effect of thiazides is achieved with small dosages (6.25 to 25.0 mg daily), which have a small effect on K^+ balance; consequently, high dosages of thiazides are not warranted because they will result in K^+ depletion without better blood pressure control. Insulin administration in the course of treating DKA, a condition in which K^+ depletion is usually present, can result in profound and symptomatic hypokalemia.

K^+ Overload with Hyperkalemia. Potassium overload leading to hyperkalemia can occur because of increased K^+ intake or decreased renal K^+ excretion. The former occurs when the adaptive increase in renal K^+ excretion is insufficient to match the larger-than-normal K^+ intake. Salt substitutes are K^+ salts (KCl) that mimic the taste of NaCl and their use may lead to hyperkalemia. As these products are available over the counter, patients frequently use them whether they are recommended by physicians or not. A low NaCl intake reduces the ability of the kidney to excrete K^+; simultaneous ingestion of salt substitutes (K^+ salts) can lead to hyperkalemia owing to the combination of increased K^+ intake and reduced renal K^+ excretion. In fact, a low NaCl intake is the single most commonly observed contributing factor in the development of hyperkalemia in clinical practice. Removing the salt restriction promotes increased kaliuresis, which might partially or fully correct the hyperkalemia.

Diabetes mellitus commonly damages the renal mechanisms of potassium excretion.[34] Such abnormality might result from decreased GFR, decreased tubular secretion of K^+, hypoaldosteronism or pseudohypoaldosteronism, or drugs. In the absence of generalized renal failure, a diminished renal K^+ excretion reflects either a defect in the renin–angiotensin–aldosterone axis or renal resistance to aldosterone.

Renin deficiency leads to a low plasma aldosterone level that might reduce renal K^+ excretion. It occurs in certain physiologic states (advanced age, expansion of ECF volume), with the use of various drugs (β-adrenergic blockers, inhibitors of prostaglandin synthesis, methyldopa), with certain toxins (lead), in some systemic diseases (diabetes mellitus), and in some renal diseases (obstructive uropathy, interstitial nephritis). A common cause of renin deficiency is the so-called type 4 renal tubular acidosis, which is characterized by impaired excretion of both K^+ and H^+. Perhaps its most common presentation is in elderly diabetic patients. Angiotensin-converting enzyme (ACE) inhibitors lead to hypoaldosteronism, which reduces renal K^+ excretion and can increase $[K^+]_p$.

One or more of the various syndromes of diminished aldosterone activity may be observed in diabetes mellitus. A diminished aldosterone activity can occur as a result of:

1. A primary defect in the adrenal synthesis of aldosterone owing to a disease or defect in the adrenal cortex.
2. A secondary defect in the adrenal synthesis of aldosterone owing to failure in the production, release, or action of the various components of the renin-angiotensin-aldosterone axis (e.g., renin deficiency).
3. End-organ resistance to aldosterone, owing to either drugs acting on the kidney (e.g., spironolactone) or renal disease.

Drug-induced mechanisms of hypoaldosteronism leading to hyperkalemia are commonly encountered in diabetic patients. Prostaglandin synthetase inhibitors, such as the nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclosporine inhibit renin secretion, producing hyporeninemic hypoaldosteronism. These drugs can also cause hemodynamically induced decreases in GFR as well as direct nephrotoxicity, thereby impairing further K^+ excretion. ACE inhibitors decrease plasma levels of angiotensin II resulting in decreased levels of aldosterone. Heparin acts directly on the adrenal gland, inhibiting aldosterone secretion. Increased $[K^+]_p$ can occur with heparin administration in approximately 5% of hospitalized patients.

Diabetes mellitus is also associated with end-organ resistance to aldosterone, leading to hyperkalemia, a syndrome known as pseudohypoaldosteronism. This entity can develop as a result of drug administration or renal diseases. Hyperkalemia caused by spironolactone, eplerenone, triamterene, and amiloride, collectively known as K^+-sparing diuretics, exemplifies drug-induced pseudohypoaldosteronism. Renal diseases that primarily damage the renal tubules (with minor decreases in GFR), collectively known as tubulointerstitial renal diseases, elicit this hyperkalemic syndrome (e.g, obstructive uropathy).

Diabetes mellitus is the single major cause of end-stage renal disease (ESRD), and therefore commonly leads to hyperkalemia because of decreased renal function (diminished GFR). In the presence of renal insufficiency, potassium balance might be maintained within normal limits until the GFR decreases to less than 25% of normal. The ability of the kidney with decreased GFR to maintain K^+ balance depends on the development of compensatory mechanisms, collectively known as K^+ adaptation, that increase the fractional K^+ excretion (FE_K) by the kidney.[34] Because $[K^+]_p$ might remain within normal limits in patients with only 25% of overall renal function (GFR), whereas K^+ intake remains unchanged, a fourfold increase in $FE_K{}^+$ must be present. As the calculated FE_K in normal individuals amounts to approximately 10%, the estimated FE_K in a patient with this degree of renal insufficiency is about 40%.

Management of Hyperkalemia. The management of K^+ retention should be initiated even in the presence of a mild degree of hyperkalemia.[34] Several measures should be undertaken at once in patients who have high-normal $[K^+]_p$ (i.e., 5.0 mEq per L) and a disease that predisposes to hyperkalemia, such as diabetes mellitus with renal dysfunction. Severe restriction of dietary NaCl intake should be avoided because it impairs renal K^+ excretion; dietary NaCl intake should be at least 4 g per day. Restriction of dietary K^+ must be enforced. Medications that impair the renal excretion of K^+, such as K^+-sparing diuretics, should be discontinued. Metabolic acidosis, if present, should be treated with alkali therapy.

Proper management of simultaneous retention of Na^+ and K^+ in patients with diabetes mellitus and a salt-retaining disease (hypertension, congestive heart failure, nephrotic syndrome, renal insufficiency), who have an elevated $[K^+]_p$ or even a high-normal $[K^+]_p$ (i.e., 5.0 mEq per L), is effectively achieved by avoiding severe restriction of dietary NaCl intake while concomitantly administering diuretics (e.g., furosemide, thiazides). This recommendation with respect to the dietary NaCl intake should be instituted once a large ECF volume excess is no longer present. A moderate dietary NaCl intake of about 4 g per day will not result in ECF volume expansion if increased urine excretion of NaCl is achieved with the use of diuretics. This strategy secures adequate kaliuresis. Diuretics should not be administered to patients with ESRD because a meaningful kaliuretic response is not expected. A negative external K^+ balance is achieved in all patients with ESRD by: (1) the utilization of cation exchange resins (such as Kayexalate, a sodium polystyrene sulfonate) that promote the excretion of K^+ in the stools, and (2) dialysis (hemodialysis or peritoneal dialysis).

Hyperkalemia is the major threat to life in patients with type 4 renal tubular acidosis; therefore, the main focus of attention should be placed on correcting this electrolyte abnormality. That is the reason why dietary K^+ restriction, diuretics (furosemide, thiazides), and K^+-binding resins are so valuable in these patients. The intake of NaCl should be encouraged, because the availability of Na^+ in the collecting tubules is a major determinant of renal K^+ excretion. The administration of fludrocortisone (Florinef) in daily doses of 0.1 to 0.3 mg helps in the correction of hyperkalemia and acidosis (enhances distal acidification), yet the associated volume expansion may induce hypertension or increase its severity. Alkali therapy (1 to 2 mEq/kg/day) is useful to ensure correction of hyperkalemia and acidosis.

The following three strategies must be considered whenever severe hyperkalemia is present in any patient[34]:

1. To counterbalance the effect of hyperkalemia on the excitability of myocardial and skeletal muscle. This modality is not aimed at reducing the increased $[K^+]_p$.
2. To modify internal K^+ balance, promoting the translocation of K^+ from ECF to ICF. This modality will not alter the total body K^+ stores.
3. To modify external K^+ balance, inducing a net K^+ loss from the body.

The treatment of hyperkalemia with agents that ameliorate the effects of hyperkalemia on myocardial and skeletal muscle excitability involves the administration of Ca^{2+} salts (chloride or gluconate). These agents diminish tissue excitability by widening the difference between resting and threshold potentials. Calcium gluconate (20 mL of a 10% solution) can be infused intravenously over a 10-minute period. The intravenous administration of Ca^{2+} salts is definitely indicated when $[K^+]_p$ reaches 7.0 mEq per L or when significant electrocardiographic abnormalities (absence of P waves, prolongation of QRS complexes, etc.) are present. The effects of Ca^{2+} infusion are short lasting, with peak effect noted about 5 minutes after infusion.

The most important therapeutic agent that promotes cellular K^+ entry is insulin. Insulin leads to tissue uptake of K^+ as well as glucose; therefore, the latter must be infused to prevent hypoglycemia in patients presenting without hyperglycemia. Considering that hyperglycemia of endogenous and exogenous origin can result in hyperkalemia (especially in diabetics), caution should be exercised as to the rate of glucose infusion. Consequently, a situation that mimics a euglycemic insulin clamp (providing enough exogenous glucose to maintain normal plasma glucose level during insulin administration) must be instituted. Additional but less important strategies that might translocate K^+ from ECF to ICF are administration of β_2 agonists and infusion of sodium bicarbonate.

The first two modalities in the therapy of hyperkalemia are only temporary measures that remove the immediate threat to life resulting from hyperkalemia. Achievement of a net K^+ loss is the most effective therapeutic modality to reduce and sustain a normal $[K^+]_p$ in patients with severe and persistent hyperkalemia. Consequently, treatment of severe and persistent hyperkalemia must combine all three modalities.

The presence of associated clinical and laboratory abnormalities can prevent use of one or more treatment modalities of hyperkalemia. The use of K^+ exchange resins by oral or rectal routes is contraindicated in patients with significant gastrointestinal symptoms. Calcium infusions are contraindicated in patients with hypercalcemia. Sodium bicarbonate infusions are contraindicated in patients with alkalemia, patients with high $[HCO_3^-]_p$, those with hypernatremia, or in patients at a significant risk of developing pulmonary edema or with significant ECF volume expansion. Severe hyperkalemia accompanied by preserved renal function usually can be corrected without dialysis. Potassium removal can be achieved in these patients by inducing an enhanced kaliuresis with the administration of fluids containing NaCl or $NaHCO_3$, or both, and with the use of diuretics. The majority of patients who develop severe hyperkalemia, however, have renal failure, and dialysis is the treatment of choice.

Defect in Phosphate Homeostasis

The osmotic diuresis of hyperglycemia leads to decreased renal reabsorption of phosphate accounting for phosphate depletion in DKA.[45] Nonetheless, serum phosphate levels are usually normal or increased at presentation (Table 74.2). The initial serum phosphate correlates positively with serum osmolality, glucose, and anion gap. Insulin deficiency and metabolic acidosis induce a shift of phosphate from cells to the extracellular compartment thereby masking phosphate depletion. Insulin therapy shifts phosphate back into cells, rapidly lowering the serum levels.[46–48]

Defect in Acid–Base Balance

Ketoacidosis and Hyperchloremic Metabolic Acidosis. Although the metabolic acidosis of DKA is mostly caused by the overproduction of β-hydroxybutyric and acetoacetic acids, additional acids, including lactic acid, free fatty acids, and other organic acids, can contribute to the fall in plasma $[HCO_3^-]$.[5] Insulin deficiency, coupled with counterregulatory hormone excess (largely glucagon), activates cAMP, which in turn leads to phosphorylation and activation of lipase in adipocytes, thereby promoting lipolysis.[49–52] Lipolysis of triglyceride stores in the adipocyte provides long-chain fatty acids, which are the principal substrate for hepatic ketogenesis.[53,54] However, hepatic triglycerides might also serve as a source of fatty acids in the presence of fatty liver, a not uncommon condition in patients with diabetes.[5]

Role of Fatty Acid Oxidation. In addition to augmented substrate in the form of long-chain fatty acids, development of substantial ketogenesis by the hepatocyte mitochondria requires a major increase in fatty acid oxidation. A transport system, the carnitine shuttle, is needed for long-chain fatty acids to enter the mitochondrial matrix. This carrier system consists of two carnitine palmitoyl-transferases (CPT)—an outer CPT I and an inner CPT II—and carnitine/acylcarnitine translocase. The key regulatory step for fatty acid oxidation takes place in a transesterification reaction catalyzed by CPT I.[53,55] This enzyme controls the entry of acyl-coenzyme A (CoA) esters, which are derived from the long-chain fatty acids, from the cytosol into the mitochondria (Fig. 74.4).[5] In the normal fed state and in well-controlled diabetes, CPT I is inhibited such that fatty acids cannot enter the mitochondria for oxidation and ketoacid formation, but are re-esterified to triglycerides and transported out of the cytosol as very-low-density plasma lipoproteins. Inhibition of CPT I is provided by malonyl-CoA, a metabolite whose level is dependent on adequate glycolysis and activity of acetyl-CoA carboxylase.[56–59] The concentration of malonyl-CoA is maximal in the fed state, but it sharply decreases with fasting and uncontrolled diabetes. In these conditions, an increase in the glucagon/insulin ratio blocks glycolysis and inhibits acetyl-CoA carboxylase, two processes that lead to a major drop in malonyl-CoA levels. Consequently, CPT I activity is enhanced, allowing conversion of the acyl-CoA esters of long-chain fatty acids to acylcarnitines that can be transported toward the interior of mitochondria.[60] The transesterification to acylcarnitine is then reversed by CPT II, which works in conjuction with the translocase, allowing the release of fatty acyl-CoA in the mitochondrial matrix. The capacity of the hepatocytes for fatty acid oxidation is large and most of the fatty acyl-CoA molecules entering the mitochondria are oxidized to ketone bodies.

The Anion Gap. During the development of DKA, ketoacids released into the body fluids are titrated by HCO_3^- and other body buffers.[61–65] As a result of this buffering process, HCO_3^- ions are replaced by ketoanions in the extracellular fluid producing the characteristic increase in plasma unmeasured anions (the so-called "anion gap"). In uncomplicated DKA, the increment in the anion gap (AG) above its normal value should be approximately equal to the decrement in plasma $[HCO_3^-]$.[61,64] Thus, the ratio of excess AG

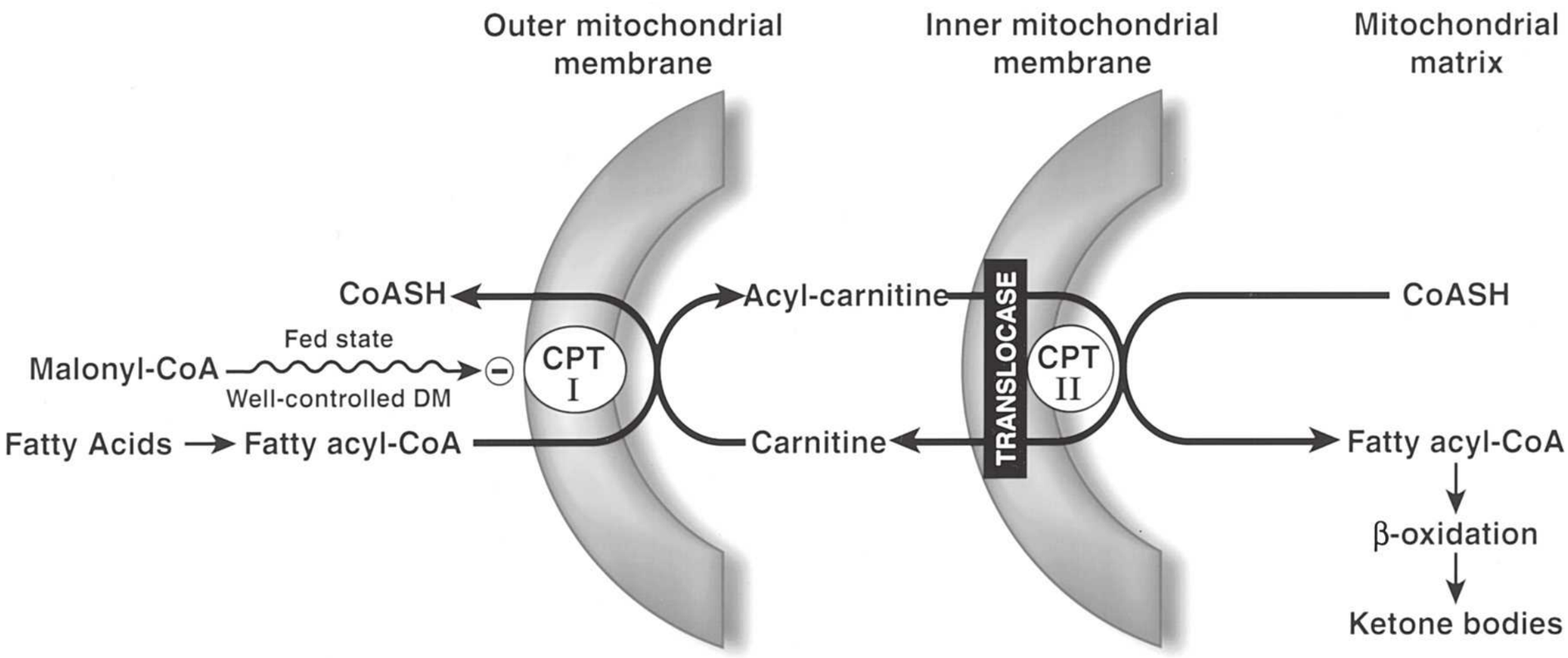

FIGURE 74.4 Regulation of hepatic ketogenesis. Synthesis of ketones in the liver depends on transfer of fatty acyl-CoA into the mitochondria by carnitine palmitoyl-transferase I (CPT I). In the fed state and in well-controlled diabetes, CPT I activity is inhibited by cytoplasmic malonyl CoA. During fasting and in patients with uncontrolled diabetes, the increase in the glucagon/insulin molar ratio suppresses malonyl CoA synthesis, allowing for increased transfer of fatty acyl-CoA into the mitochondria and increased ketogenesis. (From Foster DW, McGarry JD. Acute complications of diabetes mellitus: ketoacidosis, hyperosmolar coma, and lactic acidosis. In: DeGroot LJ, Jameson JL. *Endocrinology*. 4th ed.; 2001.)

(i.e., measured AG minus normal AG) in mEq/L to the decrement in $[HCO_3^-]$ (i.e., normal plasma $[HCO_3^-]$ minus measured plasma $[HCO_3^-]$) should be approximately 1.0. In fact, this pattern is seen in most patients with DKA.[64,66–72] Table 74.3 presents admission data obtained or calculated from several published reports of patients with DKA. Note that the mean decrement in plasma $[HCO_3^-]$ was essentially equal to the mean excess AG in most of these studies (in two studies, ΔAG actually exceeds Δ$[HCO_3^-]$ by 6 to 8 mEq per L, most likely due to a preexisting metabolic alkalosis).

74.3 Comparison of Admission Data in Diabetic Ketoacidosis

	Danowski et al.[66] (n = 8)	Seldin et al.[67] (n = 10)	Nabarro et al.[68] (n = 7)	Shaw et al.[69] (n = 30)	Assal et al.[70] (n = 9)	Oh et al.[71] (n = 35)	Adrogué et al.[64] (n = 150)[a]
Blood pH					7.06 ± 0.03	7.07 ± 0	7.06 ± 0.0
$[Na]_p$, mEq/L	130 ± 3.2	129 ± 3.7	136 ± 0.5	131 ± 1.4	146 ± 3.0	136 ± 1.6	132 ± 0.6
$[K]_p$, mEq/L	4.9 ± 0.5	4.7 ± 0.2	5.7 ± 0.2	5.8 ± 0.3	5.6 ± 0.3		5.7 ± 0.1
$[Cl]_p$, mEq/L	94 ± 2.8	94 ± 3.5	93 ± 1.0	96 ± 1.3	106 ± 3.0	101 ± 1.4	98 ± 0.6
$[HCO_3]_p$, mEq/L	7.0 ± 0.8	7.4 ± 1.0	7.5 ± 1.1	5.0 ± 0.6[a]	5.6 ± 1.0	9.6 ± 0.3	6.2 ± 0.2[a]
Anion gap, mEq/L	34.3 ± 1.3	32.1 ± 1.5	40.8 ± 2.1	36.7 ± 1.7	40.0	25.0 ± 1.2[b]	33.5 ± 0.6
Δ$[HCO_3]_p$, mEq/L[c]	17.0 ± 0.8	16.6 ± 1.0	16.5 ± 1.1	22.0 ± 0.6[a]	18.4	14.4 ± 0.3	20.8 ± 0.2
ΔAnion gap, mEq/L[d]	18.3 ± 1.3	16.1 ± 1.5	24.8 ± 2.1	20.7 ± 1.7	24.0	13.0 ± 0.9	17.5 ± 0.6

[a] TCO_2 was measured.
[b] The value was calculated with $[K]_p$.
[c] The values were derived using a baseline value of either 24 mEq/L or 27 mmol/L depending on whether $[HCO_3]_p$ or TCO_2 were measured, respectively.
[d] The values were derived using a baseline value of 16 mEq/L.

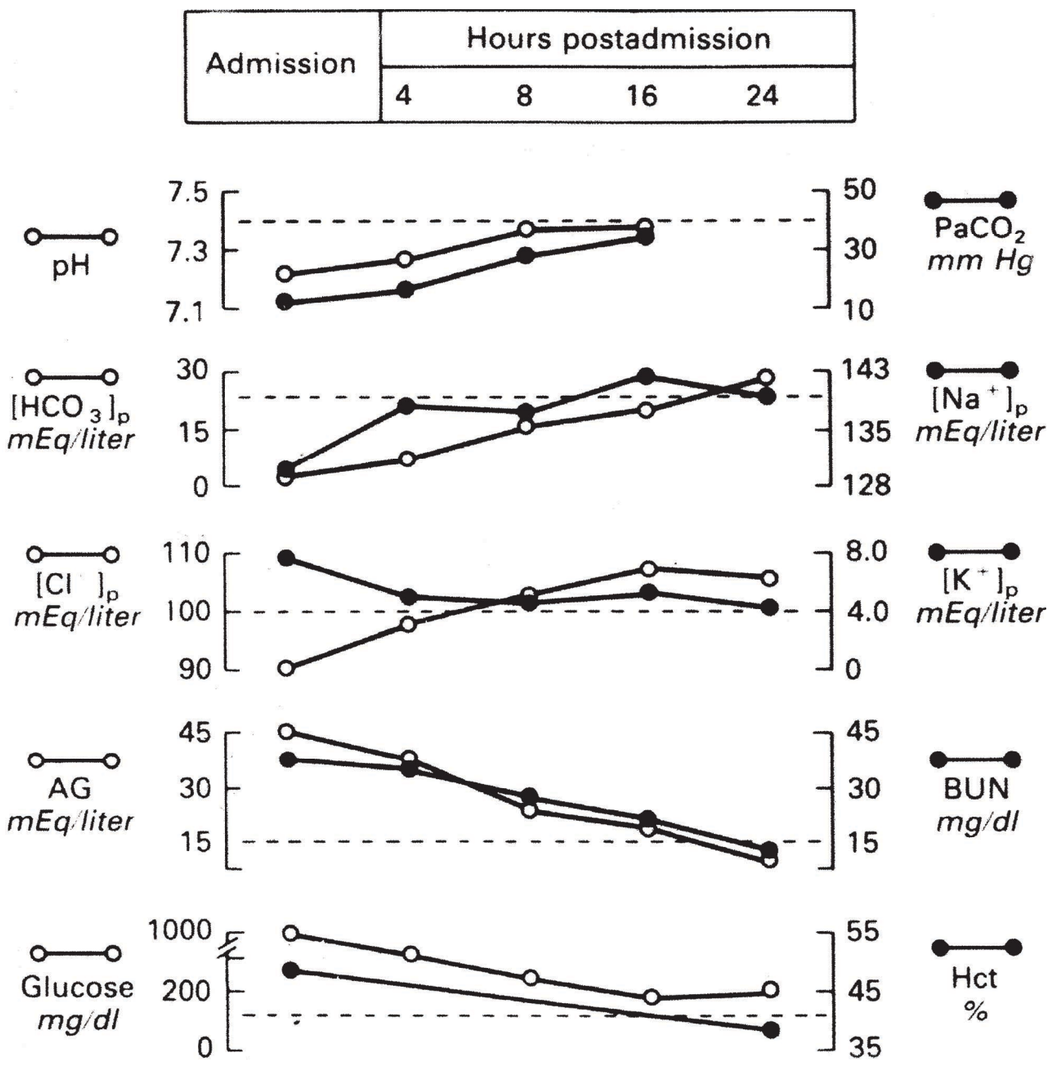

FIGURE 74.5 Laboratory data on admission and follow-up values in a patient admitted for diabetic ketoacidosis and featuring pure anion gap acidosis. Each symbol represents a single measurement. (From Adrogué HJ, Eknoyan G, Suki WN. Diabetic ketoacidosis: role of the kidney in the acid–base homeostasis re-evaluated. *Kidney Int.* 1984;25:591.)

Figure 74.5 charts the course of treatment in a patient with DKA presenting with a typical high AG acidosis.[72] In this patient, the decrement in plasma [HCO_3^-] was essentially equal to the increase in AG before treatment was begun. During the course of therapy, plasma [HCO_3^-] increased as the AG fell, and serum [Cl^-] rose concomitantly. By 16 hours after admission, serum [HCO_3^-] was 16 mEq per L, and blood pH was almost normal. Of note, the BUN was increased on admission, reflecting a prerenal fall in renal function, which was corrected by treatment (see later text).

Although most patients with DKA have an increased AG, one occasionally encounters a patient with pure hyperchloremic metabolic acidosis.[32,73] The presenting data and course of treatment in one such patient are depicted in Figure 74.6.[72] Severe metabolic acidosis, accompanied by the appropriate respiratory response, was present on admission, but the decrement in plasma [HCO_3^-] was not associated with an increase in the AG (AG = 16 ± 4 mEq per L in this example, which includes [K^+] in the calculation). A notable additional feature is that the BUN concentration is within normal limits. Despite standard treatment, 60 hours elapsed before the serum [HCO_3^-] rose to 17 mEq per L. Serum [Cl^-], although elevated on admission, increased further during treatment, and was associated with a reciprocal decrement in the AG. The fall in the AG was due, at least in part, to a major reduction in the serum protein concentration. Thus, two differences are noteworthy in patients with DKA and a normal AG. The first is that there is less evidence of impairment of renal function, and the second is a slower recovery from metabolic acidosis compared with patients presenting with an increased AG. Considering that the DKA patient is unable to properly metabolize ketoacids, whether ketoanions are retained in the ECF or are wasted in the urine should have no major effect on the severity of the acid–base disorder.

The representative cases depicted in Figures 74.5 and 74.6 portray the extremes of the acid–base patterns observed on admission for uncomplicated DKA.[72] In fact, most patients have elements of both increased AG and hyperchloremic acidosis with one element being dominant (Table 74.4). Although various factors could potentially alter the stoichiometric relationship between the increment in AG and the decrement in plasma bicarbonate, the overall level of renal function appears to be the major determinant of the type of metabolic acidosis encountered on admission for DKA.

Additional conditions might alter the ratio of excess AG/bicarbonate deficit in patients with DKA, including hyperproteinemia, vomiting, exogenous bicarbonate therapy, and hypocapnia. Differences in the apparent distribution volume of bicarbonate and ketone anions have also been proposed to explain the hyperchloremic acidosis of DKA; this hypothesis, however, has not been verified experimentally.[64]

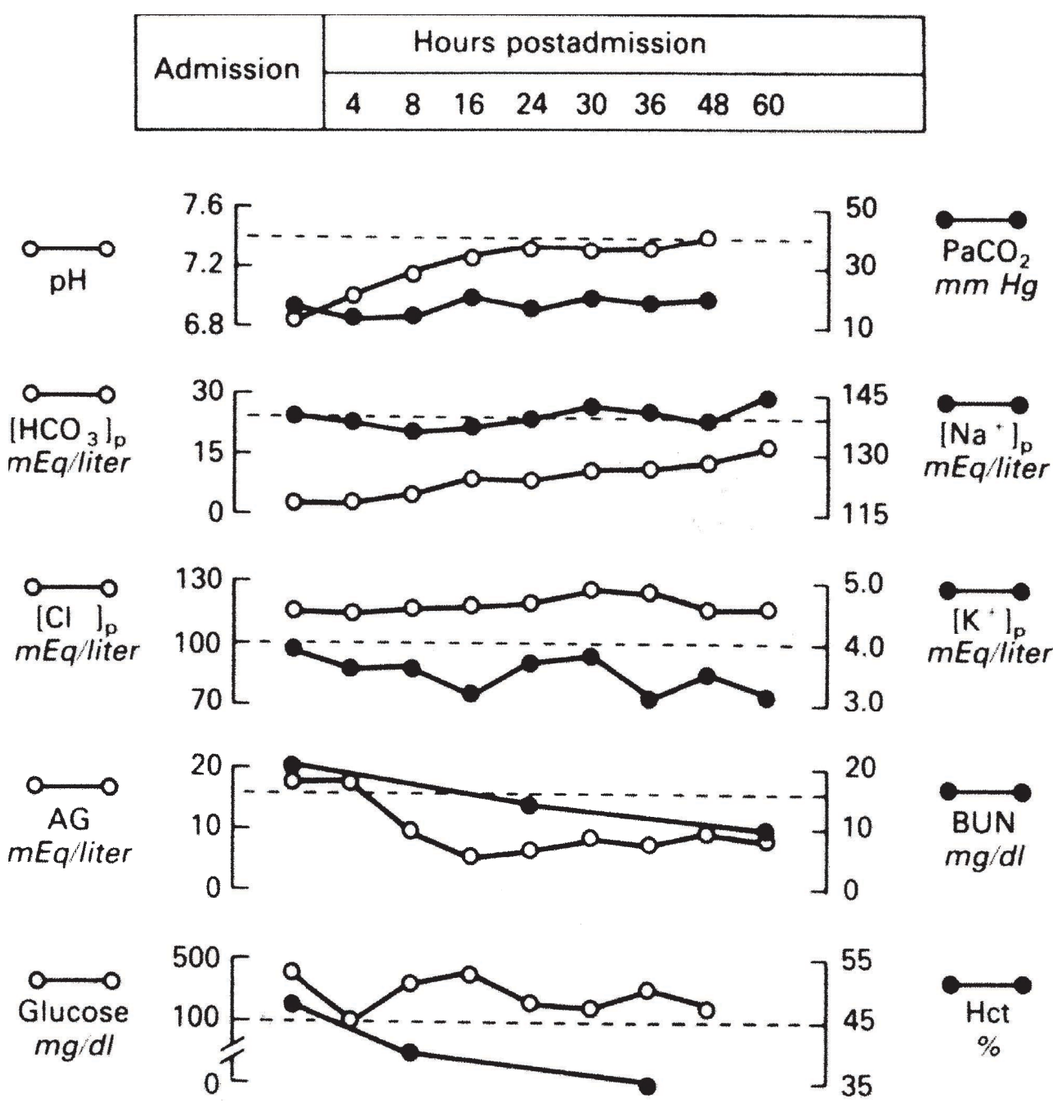

FIGURE 74.6 Laboratory data on admission and follow-up values in a patient admitted for diabetic ketoacidosis and featuring pure hyperchloremic acidosis. Each symbol represents a single measurement. (From Adrogué HJ, Eknoyan G, Suki WN. Diabetic ketoacidosis: role of the kidney in the acid–base homeostasis re-evaluated. *Kidney Int.* 1984;25:591.)

74.4 Acid–Base Patterns of Patients with Diabetic Ketoacidosis

	Pure High Anion Gap Acidosis	Mixed Forms	Pure Hyperchloremic Acidosis
Associated clinical features before start of therapy			
Fluid intake	Poor	☐	Adequate
Extrarenal fluid loss	Present	☐	Absent
ECF volume deficit	Severe	☐	Mild
Impairment of renal function	Severe	☐	Mild
Associated laboratory features before start of therapy			
Hematocrit, hemoglobin, serum proteins	Higher	☐	Lower
BUN, creatinine, uric acid	Higher	☐	Lower
Cause of changes in $\Delta AG/\Delta HCO_3$ after initiation of therapy[a]	Bicarbonate administration	☐	Infusion of chloride-rich solutions

[a]AG, anion gap; AG, $[Na^+]_p - ([Cl^-]_p + [HCO_3^-]_p)$. Excess AG (mEq/L) equals measured AG minus normal AG, and bicarbonate deficit (mEq/L) equals normal plasma bicarbonate minus measured plasma bicarbonate. Expected value of $\Delta AG/\Delta HCO_3^-$ is 1.0 as the bicarbonate deficit is the result of its titration by ketoacids.
ECF, extracellular fluid; BUN, blood urea nitrogen.

Role of the Kidney in Modulating the Anion Gap. Because renal reabsorption of filtered plasma ketoanions is limited and the production of ketoacids can reach levels as high as 1,000 to 2,000 mEq per day, the urinary excretion of the sodium and potassium salts of the ketoacid anions can be enormous.[67,68,74–76] The renal "wasting" of ketone salts in association with glucosuria-induced osmotic diuresis, poor fluid intake, and vomiting result in ECF volume depletion and a resultant reduction in renal function. Renal blood flow and GFR both fall during DKA, with recovery to normal values following the episode.[77,78] Increased urea production from enhanced catabolism of amino acids in patients with DKA also contributes to the elevation of blood urea nitrogen levels.

Patients with DKA who develop substantial volume depletion will tend to present with an increased AG metabolic acidosis because of their limited ability to excrete ketone salts. Conversely, patients with DKA who are able to maintain sodium and water intake, thereby minimizing ECF volume depletion, will tend to present with variable degrees of hyperchloremic acidosis, due to urinary excretion of ketone salts and retention of chloride.[64,72]

Effect of Treatment on Anion Gap. Volume replacement with saline infusions during treatment of DKA causes dilution of both ketones and bicarbonate; thus, the AG decreases due to replacement of an unmeasured anion (ketones) with a measured anion (Cl^-). Additionally, correction of K^+ depletion with the chloride salt results in the cellular uptake of K^+ in exchange for H^+, whereas most of the chloride remains in the ECF. Because the H^+ extruded is titrated by HCO_3^-, the net effect is the development of hyperchloremic acidosis.

Renal Response to Ketoacidosis. Diabetic ketoacidosis stimulates renal acid excretion, leading to a several-fold increase in net acid excretion. It should be recalled that a voltage-dependent stimulus for H^+ secretion exists in the distal nephron whenever sodium is absorbed without an accompanying anion. A substantial electrical gradient favoring distal H^+ secretion is present in DKA as a result of increased distal sodium delivery (ketonuria and osmotic diuresis), avid sodium reabsorption (ECF volume contraction), and the presence of poorly reabsorbable anions (ketones). As a result, daily renal net acid excretion, as ammonium and titratable acid, can attain levels as high as 250 and 500 mEq, respectively.[75] Although this vigorous response suggests that the kidney very effectively defends acid–base homeostasis in the course of DKA, such a conclusion is untenable. Maximal stimulation of renal acidification in DKA does not suffice

to compensate for the large urinary loss of HCO_3^- precursors in the form of salts of ketoacids. In fact, experimental studies have shown that despite maximal stimulation of urinary acidification, for each mmol of β-hydroxybutyrate excreted, the kidney could salvage only about 0.5 mEq of potential base.[79] Although ketones have been shown to inhibit the rate of renal ammoniagenesis in the experimental animal, this effect most probably plays only a minor role in humans, as a large increment in urinary ammonium excretion is present in DKA.[80]

Effect of Treatment on Renal Response. Balance studies carried out in the early period after admission for DKA revealed that correction of volume depletion resulted in massive urinary loss of bicarbonate precursors (salts of ketoacids) that exceeded the elevated levels of urinary ammonium and titratable acidity (Table 74.5).[72] Thus, in the initial period after admission, the kidneys behave in a maladaptive fashion relevant to the systemic acid–base composition.[72] Only when the plasma ketones have fallen substantially is stimulation of urinary excretion of ammonium and titratable acidity capable of generating sufficient new HCO_3^- to begin to correct the ketoacidosis.

Lactic Acidosis. Patients with diabetes mellitus may develop lactic acidosis, which represents a potentially serious condition.[81] Its diagnosis is warranted in the presence of a high anion gap metabolic acidosis associated with blood lactate levels equal to or higher than 4 mEq per L. This acid–base disorder results from the imbalance between production and utilization of lactate; thus, lactic acidosis might result from increased production, decreased utilization, or both. The skeletal muscle and gut are the organs involved in the development of lactic acidosis because of overproduction. The liver and, to a lesser degree, the kidney are the organs playing the major role in lactate removal. Diabetes mellitus has been shown to be associated with type A as well as type B lactic acidosis. However, this classification has lost its appeal in clinical practice because patients frequently display features of type A as well as type B lactic acidosis simultaneously.[82] Type A includes clinical conditions associated with impaired tissue oxygenation. Examples of type A lactic acidosis are clinical states with either reduced oxygen delivery (shock, cardiac arrest, severe hypoxemia, and sepsis) or those with increased oxygen demand (vigorous exercise, shivering, and generalized seizures). Type B includes clinical conditions in which there is no apparent oxygenation defect to explain the hyperlactatemia. Although patients with type A acidosis develop clinical signs of tissue hypoxia or underperfusion, patients with type B lactic acidosis lack these manifestations. Examples of type B acidosis include congenital defects in glucose or lactate metabolism and many

74.5 Role of the Kidney in the Acid–Base Defense in Normal Subjects and During Recovery from Diabetic Ketoacidosis

	Normal Subjects[a] $TA + NH^+_4 - HCO_3^-$		Diabetic Ketoacidosis[b] $TA + NH^+_4 - HCO_3^-$[c]	
	Balance	Cum. balance	Balance	Cum. balance
Post admission	**mEq**		**mEq**	
0 to 4 hours	12.7	12.7	−45.0 ± 8.2	−45.0 ± 8.2
4 to 8 hours	12.7	25.4	−10.3 ± 13.5	−55.3 ± 20.8
8 to 12 hours	12.7	38.1	1.8 ± 6.8	−53.5 ± 27.1
12 to 16 hours	12.7	50.8	−16.5 ± 2.0	−37.0 ± 28.3
16 to 20 hours	12.7	63.5	−14.3 ± 2.3	−22.7 ± 28.9
20 to 24 hours	12.7	76.2	−21.2 ± 4.8	−1.5 ± 31.2

[a]Estimate based on net acid excretion equal to 1.25 mEq/kg body weight/day and a body weight equal to that of the diabetic patients (61 kg).
[b]The values presented are means ± 1 SE of four studies.
[c]Actual plus potential bicarbonate is shown; ketone salts other than ammonium represent potential bicarbonate.
From Adrogué HJ, Eknoyan G, Suki WN. Diabetic ketoacidosis: role of the kidney in the acid–base homeostasis re-evaluated. Kidney Int. 1984;25:591–598.

acquired conditions (e.g., diabetes mellitus, malignancies, toxins, and liver disease). Lactic acidosis caused by metabolic defects comprises: (1) disorders of glucoregulation, including hypoglycemia and diabetes mellitus; (2) major organ failure, involving hepatic, renal, or multiple organ failure; and (3) neoplasias, especially lymphomas, leukemias, sarcomas, and lung carcinomas.

Several drugs and toxins might cause lactic acidosis in diabetic and nondiabetic patients. Ethanol abuse is probably the most common cause within this group. The oral hypoglycemic agents of the biguanides group (phenformin and metformin) used to be a major cause of lactic acidosis, particularly in patients with impaired renal function; the limited worldwide use of these drugs, at the present time, explains their diminishing importance in the etiology of lactic acidosis. Many other drugs, including salicylates, methanol, ethylene glycol, propylene glycol, nitroprusside, and isoniazid, might cause this condition.

Correction of the underlying cause of lactic acidosis is the cornerstone of treatment of this condition. The high mortality associated with lactic acidosis can be reduced by securing adequate support of vital functions. The hemodynamic status and tissue perfusion might improve by correcting volume deficit, enhancing cardiac output, and avoiding vasoconstricting drugs (e.g., norepinephrine). Tissue oxygenation must be optimized by correcting anemia or providing a higher inspired oxygen mixture with or without mechanical ventilation. Energy stores must be replenished to prevent the development of hypoglycemia. If drugs or toxins are responsible for the lactic acidosis, it is mandatory to remove these agents promptly from the patient's tissues by whatever means available (i.e., hemodialysis or hemoperfusion, if necessary). Sepsis must be treated aggressively. Other measures in the management of lactic acidosis might include alkali therapy as well as the use of dichloroacetate (DCA), which enhances the oxidation of pyruvate, as described later.

The utilization of alkali therapy in the treatment of lactic acidosis is controversial because the rising pH associated with this treatment tends to further increase hyperlactatemia. It has been known for years that acidosis inhibits glycolysis, whereas alkalosis stimulates it and consequently results in elevated plasma lactate levels; this effect, however, is generally mild and usually results in an increase in plasma lactate of only 1 to 3 mEq per L. This pH feedback system is not unique to lactic acid but also occurs with other organic acids, including ketoacids, whose production is inhibited by acidosis and stimulated by alkalosis. Additionally, HCO_3^- therapy neither alters the natural course of the deranged metabolism leading to lactic acidosis nor diminishes the mortality of this condition. Yet, most experts advise HCO_3^- therapy in lactic acidosis in the presence of severe acidemia (blood pH $<$7.20) or $[HCO_3^-]_p$ lower than 10 to 12 mEq per L. Bicarbonate administration, however, has several potential adverse effects that are described elsewhere in this chapter.

Other therapeutic measures include the administration of Carbicarb (0.33 mol per L sodium carbonate and 0.33 mol per L sodium bicarbonate) and DCA. The alkalinizing capacity of Carbicarb is identical to that of $NaHCO_3$, but Carbicarb produces less carbon dioxide.[82] Thus, the potential risk of tissue acidosis owing to H_2CO_3 accumulation appears to be lower when Carbicarb is used instead of pure $NaHCO_3$. However, the use of Carbicarb in clinical practice is not universally accepted. DCA limits lactate production by stimulating pyruvate dehydrogenase activity, resulting in oxidation of pyruvate to acetyl CoA. The usual dose in adults with lactic acidosis is 50 mg per kg of body weight, diluted in 50 mL of isotonic saline for intravenous infusion over a 30-minute period. This dose might be repeated if plasma lactate levels remain substantially elevated. Limited experience with DCA indicates that this therapy can be beneficial in some cases of lactic acidosis.

Renal Tubular Acidosis. A normal anion gap acidosis, also known as hyperchloremic acidosis, might develop either from a primary loss of HCO_3^- or a failure to replenish HCO_3^- stores depleted by the daily production of fixed acids. These two defects are commonly encountered in patients with diabetes mellitus.[61] A primary loss of HCO_3^- might result from intestinal (e.g., diarrhea) or urinary losses of alkali or its precursors (e.g., ketone salts of sodium and potassium). Hyperchloremic metabolic acidosis that results from failure to replace HCO_3^- stores that have been depleted by the daily production of fixed acids is observed in diabetics with distal tubular acidosis. In this condition, the daily net acid excretion by the kidney falls short of the daily acid production, leading to metabolic acidosis owing to depletion of HCO_3^- stores. The major causes of distal renal tubular acidosis accompanied by hyperkalemia (type 4 renal tubular acidosis) include diabetic renal disease, hypoaldosteronism, obstructive uropathy, sickle cell nephropathy, and renal transplant rejection.[83]

Combination of Multiple Disturbances

The full-blown forms of DKA and NKH represent the most frequently observed acute metabolic complications of uncontrolled diabetes mellitus.[84,85] Clinicians generally consider that each of these two entities represents a distinct condition that develops in isolation from the other in the course of diabetes mellitus. In addition, major textbooks commonly describe DKA and NKH as different processes having little in common, thereby perpetuating such a notion. In fact, these conditions are closely interrelated and represent different expressions of a remarkably similar pathophysiologic process.[84–87] Mixed forms having features of DKA and NKH are observed at least as frequently as the pure forms (Tables 74.6 and 74.7). As depicted in Figure 74.7, insulin deficiency or resistance and excessive counterregulation are present in both DKA and NKH, yet the severity of these abnormalities differs in the two clinical conditions. The profound ketosis characteristic of DKA is caused by severe insulin deficiency or resistance in association with a mild degree of excessive counterregulation.

74.6 Contrasting Clinical Features of Pure Forms of Diabetic Ketoacidosis and Nonketotic Hyperglycemia[a]

Feature	Pure DKA	Mixed forms	Pure NKH
Incidence	5 to 10 times higher	□	5 to 10 times lower
Mortality	5% to 10%	□	10% to 60%
Onset	Rapid (<2 days)	□	Slow (>5 days)
Age of patient	Usually <40 years	□	Usually >40 years
Type 1 diabetes	Common	□	Rare
Type 2 diabetes	Rare	□	Common
First indication of diabetes	Often	□	Rare
Volume depletion	Mild/moderate	□	Severe
Renal failure (most commonly of prerenal nature)	Mild	□	Severe
Subsequent therapy with insulin	Always	□	Occasional

[a]Mixed forms of DKA–NKH have intermediate features denoted by the symbol □ .
DKA, diabetic ketoacidosis; NKH, nonketotic hyperglycemia.

Conversely, the profound hyperglycemia observed in NKH results from mild insulin deficiency or resistance in association with severe activation of counterregulatory hormones as well as superimposed renal failure.

The pathogenesis of ketosis and hyperglycemia in diabetes mellitus always involves the presence of either absolute or relative insulin deficiency. Such insulin deficit might occur because of augmented insulin requirements relative to a fixed insulin dosage, withdrawal of insulin therapy, or failure of the pancreatic β-cells. Resistance to insulin action also participates in the ketosis and hyperglycemia. Factors that contribute to insulin resistance include counterregulatory

74.7 Contrasting Biochemical Features of Pure Diabetic Ketoacidosis and Nonketotic Hyperglycemia[a]

Plasma Levels	Pure DKA	Mixed Forms	Pure NKH
Glucose	<600 mg/dL	□	>600 mg/dL
Ketone bodies	4+ in 1:1 dilution	□	Not 4+ in 1:1 dilution
Effective osmolality	<340 mOsm/kg	□	>340 mOsm/kg
pH	Decreased	□	Normal
$[HCO_3^-]$	Decreased	□	Normal
$[Na^+]$	Normal or low	□	Normal or high
$[K^+]$	Variable	□	Variable

[a]Mixed forms of DKA–NKH have intermediate features denoted by the symbol □ .
DKA, diabetic ketoacidosis; NKH, nonketotic hyperglycemia.

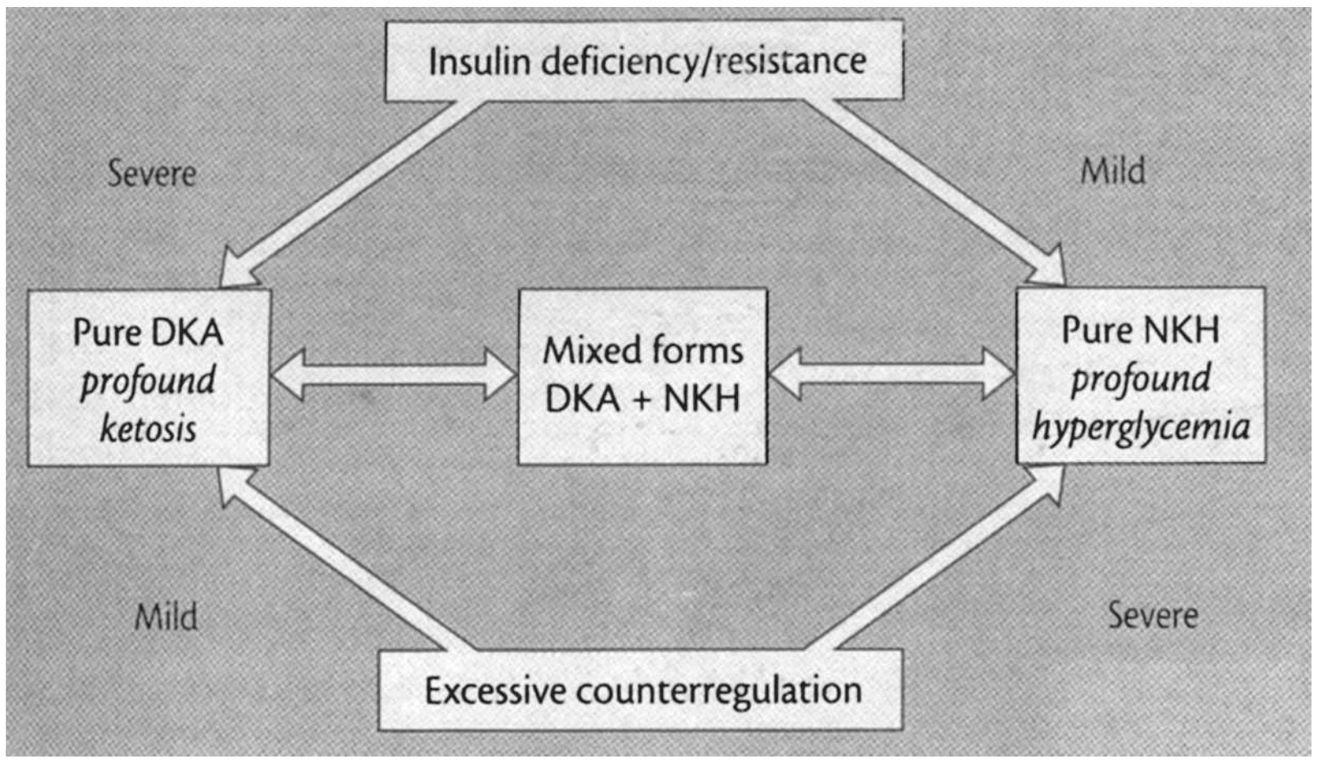

FIGURE 74.7 Diabetic ketoacidosis (DKA) and nonketotic hyperglycemia (NKH) are different forms of the same disease process.

hormones, deficiency of electrolytes (mostly potassium), increased tonicity of body fluids, and acidemia. Counterregulatory hormones play a major role in the development of hyperglycemia. Elevated levels of cortisol, growth hormone, and epinephrine depress insulin-mediated glucose uptake in peripheral tissues (e.g., skeletal muscle) and promote the release of gluconeogenic precursors from myocytes and adipocytes. The latter effect combined with augmented glucagon levels contributes to enhanced gluconeogenesis by the liver and kidney (less important role).

Figure 74.1 depicts the dominant derangements observed in the liver and peripheral tissues that are responsible for the ketonemia and hyperglycemia in decompensated diabetes. Triglycerides stored in adipocytes are decomposed into free fatty acids and glycerol by activation of a "hormone-sensitive" lipase within these cells. Whereas insulin inhibits this lipase, growth hormone, glucagon, and epinephrine stimulate its activity. Consequently, the hormonal disarray of uncontrolled diabetes augments the release of ketone precursors. The increased plasma levels of free fatty acids promote their uptake by hepatocytes where fatty acids are converted to their fatty acyl CoA derivatives. The long-chain fatty acyl CoA may be consumed in the cytosol for the synthesis of fatty acids (including malonyl CoA), triglycerides, and phospholipids (dominant pathway in the normal state) or transported by the carnitine shuttle into the mitochondria where it undergoes β-oxidation producing acetyl CoA (dominant pathway in uncontrolled diabetes mellitus). Within the mitochondria of healthy individuals, the acetyl CoA condenses mostly with oxaloacetate for oxidation in Krebs tricarboxylic acid cycle forming carbon dioxide. The alternative pathway of acetyl CoA within the mitochondria is that two molecules of this compound combine with each other to form the "ketone bodies," acetoacetate and β-hydroxybutyrate (ketoacids). The latter route is greatly stimulated in uncontrolled diabetes mellitus because oxaloacetate is in short supply (being removed from the mitochondria for the augmented gluconeogenesis) and excessive acetyl CoA cannot be accommodated through the Krebs cycle so that it overflows in the ketogenic pathway.[88] The carnitine shuttle is inhibited by cytosolic malonyl CoA, which is produced during fatty acid synthesis, ensuring that newly formed fatty acids are not immediately transported into the mitochondria and broken down. Because insulin augments, whereas glucagon and catecholamines diminish, the concentration of malonyl CoA, the hormonal imbalance of uncontrolled diabetes produces low cytosolic levels of malonyl CoA, enhancing fatty acid transport toward the mitochondria and thereby stimulating ketogenesis. In summary, synthesis of ketones in the liver largely depends on transfer of fatty acyl CoA into the mitochondria by CPT I. In the fed state of normal individuals, CPT activity is inhibited by cytoplasmic malonyl CoA. During fasting and in patients with ketoacidosis, malonyl CoA synthesis is suppressed, allowing for increased transfer of fatty acyl CoA into the mitochondria and increased ketogenesis. Decreased consumption of ketone bodies by peripheral tissues also contributes to the high levels of plasma ketones in DKA.

Clinical Manifestations and Diagnosis of Diabetic Ketoacidosis

Diabetic ketoacidosis is a medical emergency most often observed in type 1 diabetes. Less frequently, DKA is the presenting condition in obese patients with newly diagnosed type 2 diabetes. In patients with uncontrolled type 2 diabetes, DKA can be observed in combination with nonketotic hyperglycemia. The risk of developing DKA in type 1 diabetics is approximately 1% to 2% each year.[90,91] The morbidity associated with DKA is dependent on the severity of the acid–base and electrolyte disturbances present. Despite advances in treatment, mortality of DKA remains approximately 7% in the United States.[91]

Precipitating Events. Omission of insulin administration or noncompliance with treatment, various forms of stress, and dietary indiscretions (especially a large alcohol intake) represent common precipitating events of DKA and NKH

74.8 Precipitating Factors for Diabetic Ketoacidosis and Nonketotic Hyperglycemia

1. Infection (urinary tract infection, pneumonia, sepsis) ~40%
2. Inadequate insulin regimen or noncompliance with treatment ~25%
3. New-onset diabetes (~15% for DKA) and previously undiagnosed disease (for NKH)
4. Acute illness and other conditions

Myocardial infarction	Cerebrovascular accident
Acute pancreatitis	Alcohol abuse
Intestinal obstruction	Complicated pregnancy
Renal failure	Endocrine disorders (thyrotoxicosis, Cushing syndrome, acromegaly)
Peritoneal dialysis (NKH)	Trauma
Stress	Surgery
Dental abscess	Drugs (e.g., cocaine, corticosteroids, thiazides)
Heavy use of concentrated carbohydrate beverages	Idiopathic (20% to 30%)
Total parenteral nutrition	

DKA, diabetic ketoacidosis; NKH, nonketotic hyperglycemia.

(Table 74.8).[92–94] In young individuals with type 1 diabetes, emotional stress can trigger repeated episodes of DKA over short intervals. Infectious illnesses often precipitate DKA and must be aggressively treated if the ketoacidosis is to be controlled. Such common etiologies include seemingly trivial viral infections as well as pneumonia, pyelonephritis, and septicemia.[73] Pregnancy, myocardial infarction, cerebrovascular accident, intra-abdominal catastrophes (including pancreatitis), K^+ depletion, and drugs such as corticosteroids can also precipitate DKA.[84]

Symptoms and Signs. Weakness, malaise, air hunger, thirst, polyuria, vomiting, and altered sensorium are commonly observed.[1–3] Severe abdominal pain secondary to ketosis (possibly a hypertriglyceridemia-induced pancreatitis) can be observed, and these patients sometimes are mistakenly triaged to surgery.[92] However, the abdominal pain can represent an independent process, such as acute appendicitis (that requires surgery) or pyelonephritis, which in turn may have precipitated DKA. Increased rate and depth of respirations, the so-called Kussmaul breathing, is an almost constant finding. Signs of volume depletion, including orthostatic hypotension, tachycardia, decreased skin turgor, and soft eyeballs, can be evident on physical examination.[95,96] Although DKA is sometimes referred to as diabetic coma, only 10% of patients are unconscious at presentation and about 20% are alert.[92] The majority of patients present, however, with a clouded sensorium. Severe obtundation, coma, or convulsions, rarely seen in pure DKA, are prominent manifestations of severe nonketotic hyperglycemia. The patient's temperature is often decreased but the presence of hypothermia does not rule out an infectious process.[95] Conversely, if fever is present, the likelihood of infection is high. A search for tooth or skin infection, perirectal abscess, or other infectious precipitating event is most important. Patients might describe experiencing the distinct taste and smell of ketones, and the examiner might notice a fruity odor in the subject's breath.

Serum Ketones. The clinical diagnosis of DKA depends on semiquantitative assessment of serum ketones with reagent sticks or tablets; reagent tablets should be powdered before use (Table 74.9). A "large" reading (4+ reaction) for ketones in plasma diluted 1:1 or greater is diagnostic of DKA—such a reading in a urine sample is not diagnostic of DKA, however, as it can be observed in other conditions, including ordinary fasting, fasting induced by an illness that has precipitated lactic acidosis or nonketotic hyperglycemia, or nonketotic hyperglycemia itself.[5] The low renal threshold for ketones accounts for the possible development of a sufficiently high urine ketone concentration in all ketotic states to be detected as a "large" test response (4+ reaction).

The semiquantitive test for ketones measures only acetoacetate and acetone (a product derived from nonenzymatic decarboxylation of acetoacetate); it does not detect β-hydroxybutyrate. The latter ketoacid is formed from the reduction of acetoacetate in a reaction utilizing nicotinamide adenine dinucleotide (NADH). Because the β-hydroxybutyrate concentration in all ketotic states is at least two to three times higher than that of acetoacetate, a relatively high plasma ketone level of at least 6 mmol per L is required to achieve a "large" test reading in an undiluted sample. Therefore, a "large" test reading in plasma diluted 1:1 or greater indicates that at least 12 mmol per L of ketones are present, a level found in DKA but rarely present in other ketotic states.[97,98] Exceptions

74.9 Diagnostic Criteria for Diabetic Ketoacidosis and Nonketotic Hyperglycemia

	DKA:			
	Mild	**Moderate**	**Severe**	**NKH**
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10 to <15	<10	>18
Urine ketones[a]	Positive	Positive	Positive	Small
Serum ketones[a]	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)[b]	Variable	Variable	Variable	>320
Anion gap[c]	>10	>12	>12	Variable
Alteration in sensorium or mental obtundation	Alert	Alert/drowsy	Stupor	Stupor/coma

[a]Nitroprusside reaction method
[b]2 [measured Na^+ (mEq/L) + glucose (mg/dL divided 18)]
[c]$Na^+ - (Cl^- + HCO_3^-)$
DKA, diabetic ketoacidosis; NKH, nonketotic hyperglycemia.
From Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetic Association. Diabetes Care. 2009;32:1335.

include a short-term fast in late pregnancy, lactating women, and some alcoholic patients.[99–102]

The altered redox state of hepatocytes observed in tissue hypoxia, ethanol ingestion, or with high rates of fatty acid oxidation increases further the ratio of β-hydroxybutyrate to acetoacetate making the semiquantitative assay less reliable for detection of ketosis. Sulfhydryl drugs, including captopril, can produce a false positive ketone test.[103] An interaction of the colorimetric assay for creatinine with acetoacetate (chromogen) results in higher measured serum creatinine levels on admission for DKA, followed by large decreases after insulin's lowering effects on ketone levels. Table 74.2 presents a summary of salient abnormalities of blood measurements in patients presenting with DKA.

Diagnosis. The diagnosis is made by recognition of characteristic symptoms and signs, coupled with biochemical features that include hyperglycemia and ketosis.[84] A commonly used but more restrictive diagnostic criterion of DKA includes a triad of hyperglycemia (plasma glucose >250 mg per dL), ketosis (serum ketones 4+ positive by the nitroprusside reaction in a dilution 1:1 or greater), and metabolic acidosis (plasma bicarbonate <18 mEq per L, blood pH <7.30). However, the hypobicarbonatemia and acidemia might be absent in DKA because of the coexistence of additional acid–base disorders.[104]

Differential Diagnosis. The differential diagnosis of DKA includes conditions with symptoms and signs related to the neurologic, gastrointestinal, or respiratory systems. Neurologic disorders include metabolic diseases (e.g., hypoglycemia, uremia, nonketotic hyperglycemia, lactic acidosis), toxic encephalopathies (e.g., ethanol, methanol, ethylene glycol, opium derivatives, other narcotics), head trauma, cerebrovascular accident, meningitis, and encephalitis. Gastroenteritis (abdominal pain, nausea, vomiting) and pneumonia (dyspnea) can also resemble DKA.

Nonketotic Hyperglycemia. Nonketotic hyperglycemia (NKH) is a syndrome characterized by the presence of severe hyperglycemia (usually >600 mg per dL) and the absence of clinically significant ketosis (Tables 74.7 and 74.9).[84,85] DKA and NKH share the same general pathogenesis—insulin deficiency/resistance and excessive counterregulation (the most important element being high glucagon levels), but the importance of each of these endocrine abnormalities appears to differ.[86,87] Pure DKA, which features profound ketosis, might emanate from severe insulin deficiency/resistance, with milder abnormalities in counterregulation (Fig. 74.7). By contrast, NKH, which features marked hyperglycemia without ketosis, appears to reflect relatively mild insulin deficiency/resistance but more intense counterregulation. The most important clinical distinction, however, is that the

74.10 Fluid Deficit and Glucose Load as Precipitating Factors of Nonketotic Hyperglycemia in Diabetes Mellitus

Condition	Physiologic Derangement	Clinical Entity
Fluid deficit	Poor water intake	
	Relatively preserved CNS function	Elderly/nursing home patients
	Major CNS abnormality	Cerebrovascular accident, subdural hemorrhage
	Increased urinary fluid loss	Large osmotic diuresis, diuretics
	Extrarenal fluid loss	
	Gastrointestinal	Gastroenteritis, peptic ulcer disease, gastrointestinal bleeding, pancreatitis
	Skin	Heat stroke, burns
Glucose load	Increased glucose intake	Highly sweetened drinks, enteral or tube-feeding; hyperalimentation, peritoneal dialysis
	Increased endogenous glucose production	
	Stress	Psychological/physical trauma
	Infection	Pneumonia, pyelonephritis, sepsis
	Major illness	Myocardial infarction
	Medication	Corticosteroids, phenytoin, calcium channel blockers[a]

[a]Phenytoin and calcium channel blockers may decrease insulin release and precipitate the nonketotic hyperglycemia.
CNS, central nervous system.

severity of the fluid deficit and secondary renal dysfunction is greater in NKH than in DKA. This finding in NKH plays a critical pathogenetic role in the profound hypertonicity observed (Table 74.9).[105–108] In some instances, a large exogenous source of glucose can be of great importance in the development of this condition (Table 74.10).[13]

Hypertonicity and Renal Dysfunction. Renal dysfunction, most commonly caused by volume depletion, must be present to generate and sustain the extreme hyperglycemia observed in most patients with NKH.[13] Fluid deficit can be caused by poor fluid intake (e.g., in patients who are frail and unable to perceive or respond to thirst because of sedation, stroke, or other causes) and/or abnormal fluid losses due to osmotic diuresis, vomiting, diarrhea, fever, or diuretics. A simple calculation demonstrates the virtual impossibility of maintaining plasma glucose levels substantially higher than 400 mg per dL in the presence of normal renal function, because of the magnitude of obligatory glucosuria.[13] In a patient with a plasma glucose of 400 mg per dL and a normal GFR, for example, the amount of glucose that escapes reabsorption (difference between plasma glucose and the "renal threshold concentration," 180 mg per dL) is approximately 400 g per day. Glucose is also removed by cellular metabolism; whole-body glucose utilization is approximately 200 g per day under euglycemic conditions, and increases in proportion to the glucose concentration even in the absence of insulin. In patients with severe hyperglycemia and adequate renal function, therefore, substantial glucose removal, on the order of 600 to 1,000 g per day, would result both from glucosuria and internal disposal. An equal amount of new glucose must enter the circulation to satisfy these demands in steady-state, severe hyperglycemia. Thus, unless the patient has an exceptionally high level of endogenous glucose production (in excess of three times the normal value observed in the fasting state) or an extremely large exogenous source of glucose is present, severe hyperglycemia cannot be sustained in the absence of renal failure. Exogenous sources of glucose include tube-feeding solutions, parenteral hyperalimentation, or peritoneal dialysis with a high glucose concentration in the dialysate. Table 74.10 summarizes the role of fluid deficit and glucose load as precipitating factors of NKH.[13]

Absence of Ketosis

There are several theories to account for the absence of substantial ketosis in NKH.[109–111] It has been proposed that in NKH there is sufficient insulin to inhibit lipolysis but not enough to stimulate peripheral glucose uptake. This theory is based on the presumed less severe insulin deficit of patients with NKH, and the known inhibition of ketosis by relatively low insulin levels. Because hypertonicity has been shown to inhibit lipolysis in vitro, it may also be partly responsible for the absence of substantial ketoacidosis in NKH.[112] A more recent explanation offered for the absence of ketosis is hepatic resistance to glucagon, such that malonyl-CoA levels do not decrease as much as in DKA.[113–115]

Diagnosis

Typically, patients with this disorder are elderly with type 2 diabetes, and present with depressed sensorium, progressing to obtundation and finally coma (Table 74.9). They may be oliguric or anuric. Patients with "pure" NKH have no acid–base abnormalities, no clinically significant ketonemia, a markedly elevated blood glucose concentration, and elevated BUN and creatinine concentrations. The diagnosis is based on the presence of severe hyperglycemia (glucose levels >600 mg per dL), hypertonicity (>320 mOsm per kg), absence of significant ketosis, and profound volume depletion.[84] A comparison of the most salient clinical and biochemical features that distinguish pure forms of DKA from NKH are displayed in Tables 74.6 and 74.7. Notably, many patients exhibit a mixed pattern with clinical and biochemical features of both DKA and NKH. These patients should be diagnosed as having DKA-NKH.[81]

Clinical Manifestations

Depression of the sensorium, somnolence, obtundation, and coma are prominent manifestations of NKH, and the degree of CNS depression correlates with the severity of serum hypertonicity.[105] Water loss from the central nervous system with brain shrinkage has been documented within 1 hour of severe hyperglycemia in experimental animals, but brain volume recovers at 4 to 6 hours. Neither ketosis nor metabolic acidosis, features that are consistently present in DKA but usually absent in NKH, produce extreme depression of the sensorium.[105] In fact, a serum tonicity (i.e., effective osmolality) of 340 mOsm per kg H_2O or higher appears to be necessary for the development of coma, and such levels are commonly observed in NKH but not in DKA.[84,105] Circulatory collapse secondary to profound volume depletion can be observed in NKH. All other symptoms and signs previously described for patients in DKA (except for dyspnea and Kussmaul respiration that arise from metabolic acidosis) may also be observed in NKH.

Assessment of Effective Osmolality

To estimate serum tonicity (effective osmolality), one should use only the sodium and glucose concentrations (effective osmolality $= 2 \times [Na^+] +$ glucose/18). Not infrequently, a comatose diabetic patient is found to have, for example, a measured osmolality of 350 mOsm per kg H_2O but the calculated effective osmolality is only 310 mOsm per kg H_2O; in this case, the patient's coma is more likely to be due to conditions other than NKH (e.g., alcohol, uremia, cerebrovascular accident). Conversely, a comatose diabetic patient who is admitted with a calculated effective osmolality of 350 mOsm per kg H_2O most likely has NKH encephalopathy. Nonetheless, one should always exclude other causes of coma. Sometimes it is difficult to establish whether a neurologic finding is a cause or effect. For example, stroke can lead to NKH, and conversely NKH can cause a cerebrovascular accident.[116–118] Rapid reversal of the neurologic syndrome with therapy for NKH indicates that the neurologic event was not the cause but the effect of this metabolic disorder.

Therapy of Diabetic Ketoacidosis and Nonketotic Hyperglycemia

The main therapeutic goals of the successful management of DKA and NKH include repletion of fluid deficit and securing an adequate circulation, reversal of the altered intermediary metabolism, correction of the electrolyte and acid–base imbalance, and treatment of the initiating event.[119–125] To accomplish these objectives, a number of requirements must be fulfilled: continuous physician availability; 24-hour access to laboratory facilities; equipment and drugs for handling medical emergencies; and maintenance of a flowchart documenting evaluations of vital signs, mental condition, serum chemistries, urine tests, insulin intake, fluid administration (intravenous and oral), urine output, electrolyte intake, and other medications. A synopsis of the bedside and laboratory procedures for the diagnosis, management, and monitoring of DKA and NKH is presented in Table 74.11.

Fluids

Intravenous saline infusion should be started at once to correct the impaired hemodynamic status and the renal dysfunction; in addition, it lowers plasma glucose levels by enchancing glucosuria and decreasing counterregulatory hormone release (catecholamines).[126,127] Isotonic saline (i.e., 0.9%, NaCl) should be infused at the fastest rate possible in patients in circulatory shock (Table 74.12). Patients who do not have an extreme volume deficit should receive about 500 mL per hour for the first four hours followed by 250 mL per hour for the next 4 hours. More rapid administration is not recommended, as it can delay correction of acidemia (see earlier) and increase the risk of cerebral edema.[127] Some experts prefer lactated Ringer's solution to minimize the increase in serum [Cl^-], but there is no evidence that such a practice is of benefit[5]; further, it has the potential of inducing rebound metabolic alkalosis, as it loads the patient with the HCO_3^- precursor, lactate. Once the patient is hemodynamically stable, the use of half-isotonic saline with the addition of 20 to 40 mEq of potassium per each L of infusate is appropriate to also secure potassium repletion.

Patients presenting with extreme volume depletion can require a fluid infusion of as much as 5 to 10 L within the first 24 hours.[128–131] Fluid challenges of this magnitude demand that the patient receive careful monitoring for signs of pulmonary edema. Central venous or pulmonary artery catheterization may be required in some patients to accurately monitor intravascular volume.

It is unwise to allow oral fluid intake in the early phase of DKA and NKH because vomiting is common, especially if acute gastric distention is present. Although efforts should be made to avoid routine bladder catheterization in patients with uncontrolled diabetes to prevent the development or exacerbation of a urinary tract infection, a catheter might be required if the patient is stuporous or urine output cannot be monitored reliably.

74.11 Procedures/Studies for Diagnosis, Management, and Monitoring of Diabetic Ketoacidosis and Nonketotic Hyperglycemia[a]

Bedside	Laboratory Procedures/Studies
1. Assess vital signs and cardiorespiratory status (every 30 minutes for 4 hours, hourly for next 4 hours, then every 2 to 4 hours) until stable 2. Assess volume status, body weight, and skin turgor 3. Assess mental status (hourly) (consider head CT scan, lumbar puncture) 4. Blood glucose (test strips) 5. Blood and urine ketones (test strips or tablets) 6. Urine output (hourly for 6 hours and every 4 hours thereafter) until stable 7. Fluid intake and output (hourly monitoring) 8. Complete flow chart 9. Electrocardiogram 10. Chest X-ray	**Blood** 1. Glucose (hourly by test strip until <250 mg/dL, then every 2 hours; confirm in laboratory every 2 to 4 hours) until stable 2. Serum electrolytes (every 2 to 4 hours) and monitoring of serum anion gap until stable 3. Venous pH, PCO_2, HCO_3^- (every 2 to 4 hours) until stable 4. Urea nitrogen, creatinine 5. Osmolality 6. Hb, WBC, and differential 7. Cardiac enzymes 8. Amylase (spuriously elevated ?) 9. Cultures **Urine** 1. Microscopy and cultures 2. Glucose, ketones

[a]The frequency of repeat tests indicated above represents general guidelines that might require adjustments depending on the patient's presentation and response to treatment.
CT, computed tomography; Hb, hemoblobin; WBC, white blood cell.

74.12 Synopsis of Intravenous Fluids and Insulin Therapy in the Management of Diabetic Ketoacidosis and Nonketotic Hyperglycemia

1. IV fluids
   Shock: fluid resuscitation with 0.9% NaCl (isotonic saline), as needed
   Moderate to severe volume depletion: 500–1,000 mL/hr isotonic saline for 4 hours, and half the initial rate for the next 4 hours
   Mild volume depletion and
   Normal or high $[Na^+]_s$ (corrected): 0.45% NaCl at 250–500 mL/hr
   Low $[Na^+]_s$ (corrected): isotonic saline at 250–500 mL/hr
   Add dextrose (i.e., 5% dextrose in 0.45% NaCl) when serum glucose is ≤200 mg/dL

2. Insulin
   Replete K^+ first if $[K^+]_s$ <3.5 mEq/L while holding insulin
   SC route (uncomplicated DKA): regular insulin 0.3 units/kg followed by 0.2 units/kg every 2 hrs
   IV route: regular insulin as IV bolus (0.1 unit/kg) followed by continuous infusion (0.1 unit/kg/hr)
   Double insulin dose if initial glucose fall <50–70 mg/dL
   Reduce insulin dose when glucose ≤200 mg/dL or change to SC
   Keep glucose 150–200 mg/dL until resolution

DKA, diabetic ketoacidosis; NKH, nonketotic hyperglycemia; IV, intravenous; SC, subcutaneous.

Insulin

All patients with uncontrolled diabetes require insulin to reverse the ketoacidosis and correct hyperglycemia.[132–134] These actions of insulin largely reflect suppression of ketone and glucose production in the liver because of insulin's anti-glucagon effect. Of lesser importance is the insulin-induced enhancement of glucose utilization in muscle and adipose tissue as well as inhibition of lipolysis. Regular insulin should be given, if possible, intravenously.[5,85]

Mild insulin resistance is virtually a constant finding, although occasionally it may be extreme.[135,136] Consequently, insulin requirements in DKA are always several-fold higher than in normal persons. A loading dose of 15 to 30 units given as a bolus on arrival is recommended to secure binding of insulin to anti-insulin antibodies that might be present in patients who have been previously treated with animal insulin, and to assure saturation of insulin receptors.[137] In patients who are markedly volume depleted, insulin therapy should be withheld for the initial 30 to 60 minutes to allow some repletion of the ECF volume with isotonic saline. In the absence of saline, insulin can exacerbate ECF volume depletion by translocating glucose into cells, thereby causing a fall in ECF tonicity and a shift of water to the ICF compartment. In fact, fluid repletion alone in the absence of insulin administration reduces plasma glucose concentration by 35 to 70 m per dL per hour.[138]

Table 74.12 presents a synopsis of insulin therapy for the management of DKA and NKH.[139–144] Although continuous intravenous insulin infusion is most commonly used, intramuscular or subcutaneous administration appears to be as effective in correcting hyperglycemia and ketoacidosis.[46] Plasma glucose should fall at approximately 5% to 10% per hour. As the glucose level approaches 300 mg per dL, 5% dextrose in water at 50 mL per hour should be included in the intravenous fluids and the plasma glucose concentration should be followed closely.

A solution containing 100 units of insulin in 100 mL of isotonic saline is commonly used, adjusting the infusion rate to secure the insulin dosage desired. Because some patients are very resistant to insulin, much larger doses might be required. In all cases, the hourly dose should be doubled if the expected reduction in the plasma glucose is not observed within a few hours. Monitoring serum ketones during therapy is unnecessary since it does not help in the adjustment of insulin dosage.[144]

Alkali

Bicarbonate administration should theoretically be unnecessary in DKA (at least in patients with predominantly increased AG acidosis) because ketones, when finally metabolized to CO_2 and H_2O, regenerate HCO_3^-.[1–3] Indeed, several studies have shown that HCO_3^- administration did nothing to improve the recovery of patients with DKA who presented with very severe acidemia (arterial pH of 6.90 to 7.10).[145,146] The administration of HCO_3^- in DKA may also have some potentially deleterious effects because it can augment hepatic ketogenesis and lead to worsening of the CNS acidosis, hypokalemia, and rebound metabolic alkalosis.[145–147]

Nonetheless, there are proponents of alkali administration. The controversy regarding its utility is based on variable assessment of the associated risks and benefits by different workers.[84,147–151] The potential advantages and disadvantages of HCO_3^- administration are summarized in Table 74.13.

Table 74.14 summarizes our recommendations in terms of indications, goals, and dose estimation for HCO_3^- administration in DKA.[151,152] After weighing the arguments, it appears that judicious administration of HCO_3^- to severely acidemic patients, especially those with predominant hyperchloremic metabolic acidosis, confers net benefit; the goal is to support the arterial pH at 7.10 to 7.20 and serum [HCO_3^-] at approximately 10 mEq per L. Bicarbonate should be added to an IV infusion, if possible, instead of administering by intravenous bolus (unless hyperkalemia is present), because of the risk of severe hypokalemia.

Potassium

The typical patient with DKA has a potassium deficit of 4 to 8 mEq per kg at the time of admission, yet the initial serum [K^+] will usually be normal or elevated (see earlier and Table 74.2). Serum [K^+] decreases with therapy because of insulin-mediated uptake by cells, dilution due to volume repletion by intravenous fluids, correction of metabolic acidosis, and urinary K^+ losses. Thus, K^+ supplementation is required.[1–3] Specifically, after the initial fluid challenge has restored the urinary output and assuming that serum [K^+] is below 5.0 mEq per L, an intravenous infusion of 10 to 20 mEq per hour should be started and continued until the DKA is controlled and serum [K^+] is 4.0 to 5.0 mEq per L. Serum [K^+] should be monitored periodically and the K^+ infusion rate adjusted, as needed. Details about K^+ supplementation are provided in Table 74.15.

Phosphate

Because phosphate administration is of unproven clinical significance and potentially dangerous (i.e., it might result in hypocalcemia and hypomagnesemia), it should not be infused unless the serum phosphate is below 0.5 mg per dL; in those circumstances, 10 to 30 mmol of potassium phosphate might be added to the intravenous infusion and repeated if necessary to correct persistent hypophosphatemia. The hypophosphatemia of DKA may have serious consequences (e.g., impaired myocardial and/or skeletal muscle contractility) if it occurs in undernourished patients, such as chronic alcoholics. In this population, parenteral phosphate replacement of 60 to 120 mmol administered over a 24-hour period is recommended.

Cerebral Edema and Other Complications of Therapy

Patients with DKA may be admitted with a relatively normal mental status and subsequently become unconscious within the first 12 hours of therapy, in spite of a partial or complete correction of the hyperglycemia and ketoacidosis.[153] These

74.13 Potential Advantages and Disadvantages of Bicarbonate Administration in the Management of Diabetic Ketoacidosis

Advantages

1. Improves hemodynamic status if shock persists after volume repletion and severe metabolic acidosis is present
2. Increases myocardial contractility and enhances cardiac and vascular responsiveness to catecholamines
3. Aids correction of hyperkalemia, especially in patients with prerenal azotemia
4. Prevents a rapid fall in CSF osmolality and therefore might decrease risk of cerebral edema
5. Aids correction of cell metabolism and function (including CNS), impaired by severe acidosis
6. Improves acidosis-induced glucose intolerance and insulin resistance

Disadvantages

1. Induces or worsens hypokalemia, leading to cardiac arrhythmias (especially in digitalized patients) and/or dysfunction of respiratory muscles (respiratory failure)
2. Produces ECF volume expansion that can cause pulmonary edema
3. Reduces cerebral blood flow (pH effect) and O_2 delivery to the brain
4. Worsens hypophosphatemia due to cellular uptake of phosphate and depresses O_2 delivery to tissues (increased affinity of Hb for O_2)
5. Produces hypernatremia and increased serum osmolality
6. Decreases further CSF pH, leading to worsening of CNS function
7. Induces overshoot (rebound) alkalosis once conversion of ketone salts to bicarbonate takes place
8. Aggravates ketogenesis and lactic acidosis
9. Predisposes to tetany resulting from hypocalcemia and alkalemia

CSF, cerebrospinal fluid; CNS, central nervous system; ECF, extracellular fluid.

74.14 Indications, Goals, and Dose Estimation for Bicarbonate Administration in the Management of Diabetic Ketoacidosis

INDICATION

1. Extreme metabolic acidosis (pH $<$7.00, TCO_2 $<$5 mmol/L), independent of prevailing hemodynamic status
2. Severe metabolic acidosis (pH $<$7.15, TCO_2 $<$10 mmol/L) in association with one or more of the following:
   - Shock unresponsive to volume repletion
   - Persistence or worsening of acidemia after several hours of therapy
   - Predominant hyperchloremic acidosis instead of the usual high anion gap acidosis
   - Worsening of mental status and CNS depression
3. Severe hyperkalemia ($[K^+]_p$ $>$7 mEq/L)

GOALS AND DOSE ESTIMATION

1. If TCO_2 $<$5 mmol/L (indication 1), it should be increased to no more than 8 to 10 mmol/L
2. If TCO_2 is 5 to 10 mmol/L (indication 2), it should be increased to no more than 13 to 15 mmol/L
3. Dose estimation: (desired plasma TCO_2 − current plasma TCO_2) × b.wt (kg) × 0.5[a]
4. Calculated bicarbonate dose can be added to IV infusion (1 to 2 ampules or 44 to 88 mEq $NaHCO_3$ per L) or given by IV bolus (50% of estimated dose immediately, and the rest within 2 to 4 hours provided that hypokalemia is not present or is simultaneously treated and that evidence of pulmonary edema is not found)
5. Monitor blood acid–base status every 30 to 60 min (for 2 to 4 hours) after initiation of bicarbonate therapy to adjust dose to patient's needs

[a]Derives from the "apparent space of distribution" of bicarbonate (retained HCO_3^- in mEq/kg divided by the $\Delta[HCO_3^-]_p$ from preinfusion) that is approximately 50% of body weight in normal subjects but higher in hypobicarbonatemic states. Thus, this formula purposefully underestimates bicarbonate requirements to avoid the risk of overcorrection.
CNS, central nervous system; IV, intravenous.

74.15 Potassium Supplementation in the Management of Diabetic Ketoacidosis and Nonketotic Hyperglycemia

KCl should not be added to the initial 2 L of IV infusion to avoid hyperkalemia because
- Urinary output is initially unknown
- Initial $[K^+]_p$ is usually normal or high

Exception to the above rule on K^+ supplementation: add K^+ to the initial 2 L of IV fluids if
- Initial $[K^+]_p$ <4.0 mEq/L and
- Adequate diuresis is secured

KCl should be added to the third L of IV infusion and subsequently if
- Urinary output is adequate (should be at least 30 to 60 mL/hr) and
- $[K^+]_p$ <5.0 mEq/L

Rate of IV K^+ supplementation:
20 to 30 mEq/hour if $[K^+]_p$ <4.0 mEq/L
10 to 20 mEq/hour if $[K^+]_p$ >4.0 mEq/L

Concentration of K^+ in IV infusions:
20 mEq/L when IV supplementation is started and subsequently if $[K^+]_p$ <4.0 mEq/L, and IV infusion rate is = 1 L/hour
40 mEq/L (maximum) if $[K^+]_p$ <4.0 mEq/L and IV infusion rate is <1 L/hour

Monitoring of K^+ supplementation is accomplished by
$[K^+]_P$ every 2 to 4 hours during the initial 12 to 24 hours of therapy
ECG every 30 to 60 minutes during the initial 4 to 6 hours (i.e., only lead II)

IV, intravenous.

patients are typically, but not exclusively, children or young adults, and their morbidity and mortality is relatively high.[154] Often, the fatal outcome is unexpected, as these patients do not have the underlying vascular, cardiac, and renal abnormalities found in older diabetics. At autopsy, cerebral edema is consistently present.[154] Although cerebral edema leading to death or chronic sequelae (e.g., isolated growth hormone deficiency) is fortunately rare, milder forms can be regularly found in the course of standard treatment of DKA.[5,155,156]

The pathogenesis of this condition remains poorly understood.[116,157–159] Osmotic disequilibrium between brain cells and the cerebrospinal fluid (CSF) is often cited as the principal determinant of cerebral edema. In response to hyperglycemia, brain cells increase their osmolar content within hours to defend themselves against shrinkage. Once this cellular adaptation to hypertonicity has occurred, a sudden decrease in CSF osmolality, due to hypotonic fluid infusions or a fall in plasma glucose, may cause swelling of these adapted cells and produce cerebral edema. Insulin administration also activates the plasma membrane Na^+/H^+ exchanger (NHE–1), which promotes sodium entry in brain cells, facilitating development of cerebral edema. The effects of rapid crystalloid volume loading in diabetic patients with DKA and the resulting dilutional hypoalbuminemia have been studied and some degree of brain swelling or increase in CSF pressure was found.[160–165] Alterations in CSF pH and oxygen tension following HCO_3^- administration may also contribute to the development of cerebral edema.

These mechanisms are only hypotheses, however, and the pathogenesis of cerebral edema in DKA remains uncertain. Still, it seems prudent in the course of therapy of DKA (and that

74.16 Complications Of Diabetic Ketoacidosis and Nonketotic Hyperglycemia

1. Cardiogenic shock
2. Septic shock
3. Cerebral thrombosis
4. Hypoglycemia
5. Hypokalemia and hyperkalemia
6. Fluid overload (pulmonary edema)
7. Cerebral edema (with possible neurologic sequelae or death)
8. Acute gastric dilatation, erosive gastritis
9. Infection: urinary tract, pneumonia, mucormycosis
10. Venous and arterial thrombosis
11. Acute tubular necrosis (renal failure)

of nonketotic hyperglycemia) to avoid excessively aggressive volume replacement, sudden changes in the patient's serum glucose and [Na^+], and excessive use of HCO_3^-.

A number of life-threatening complications may develop in the course of DKA and NKH in spite of adequate medical care (Table 74.16). Shock of cardiac origin or resulting from sepsis or volume depletion, as well as cerebral thrombosis and edema, are among the most prominent complications.[92,166] Cerebral edema leading to death or responsible for chronic sequelae[118,155] fortunately is rare, yet milder forms may be regularly found with the standard treatment of DKA[160] and NKH.[167] Mortality from DKA has declined from more than 40% in the 1930s to less than 5% in some institutions, as the result of improvements in medical technology and appreciation of the seriousness of the disease. Yet, the prognosis of patients with NKH is substantially worse, as evidenced by the higher mortality associated with this metabolic complication (10% to 60%).[85]

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