

Coma

Coma is a *medical emergency* calling for immediate evaluation to determine its cause so that proper therapy can be started. Patients with diabetes may be comatose because of hypoglycemia, diabetic ketoacidosis, hyperglycemic hyperosmolar coma, or lactic acidosis. When evaluating a comatose diabetic patient, these must be considered *in addition* to the myriad causes included in the differential diagnosis of coma (eg, cerebrovascular accidents, head trauma, intoxication with alcohol, or other drugs).

After emergency measures have been instituted (airway protection; laboratory tests; intravenous dextrose unless fingerstick blood glucose shows hyperglycemia), a careful history (from family, friends, or paramedics), physical examination, and laboratory evaluation are required to resolve the differential diagnosis. Patients in deep coma from a hyperosmolar nonketotic state or from hypoglycemia are generally flaccid and have quiet breathing—in contrast to patients with acidosis, whose respirations are rapid and deep if the pH of arterial blood has dropped to 7.1 or below. When hypoglycemia is a cause of the coma, the state of hydration is usually normal. Although the clinical laboratory remains the final arbiter in confirming the diagnosis, a rapid *estimate* of blood glucose and ketones can be obtained by the use of bedside glucose and ketone meters (see Laboratory Findings in diabetes mellitus, earlier). Table 17–20 is a summary of some laboratory abnormalities found in diabetic patients with coma attributable to diabetes or its treatment.

1. DIABETIC KETOACIDOSIS

This acute complication of diabetes mellitus may be the first manifestation of previously undiagnosed type 1 diabetes or may result from increased insulin requirements in type 1 diabetes patients during the course of infection, trauma, myocardial infarction, or surgery. The National Data Group reports an annual incidence of five to eight episodes of diabetic ketoacidosis per 1000 diabetic patients. In all cases, precipitating factors such as infection should be searched for and treated appropriately. Poor compliance, either for psychological reasons or because of

inadequate patient education, is probably the most common cause of diabetic ketoacidosis, particularly when episodes are recurrent. In adolescents with type 1 diabetes, recurrent episodes of severe ketoacidosis often indicate the need for counseling to alter this behavior.

Diabetic ketoacidosis has been found to be one of the more common serious complications of insulin pump therapy, occurring in approximately 1 per 80 patient-months of treatment.

Patients with type 2 diabetes may also develop ketoacidosis under severe stress such as sepsis, trauma, or major surgery.

Pathogenesis

Acute insulin deficiency results in rapid mobilization of energy from stores in muscle and fat depots, leading to an increased flux of amino acids to the liver for conversion to glucose and of fatty acids for conversion to ketones (acetoacetate, β -hydroxybutyrate, and acetone). In addition to this increased availability of precursor, there is a direct effect of the low insulin-glucagon ratio on the liver that promotes increased production of ketones as well as of glucose. In response to both the acute insulin deficiency and the metabolic stress of ketosis, the levels of insulin-antagonistic hormones (corticosteroids, catecholamines, glucagon, and GH) are consistently elevated. Furthermore, in the absence of insulin, peripheral utilization of glucose and ketones is reduced. The combination of increased production and decreased utilization leads to an accumulation of these substances in blood, with plasma glucose levels reaching 500 mg/dL (27.8 mmol/L) or more and plasma ketones reaching levels of 8 to 15 mmol/L or more. β -Hydroxybutyrate is the predominant ketone and its ratio to acetoacetate increases from 1:1 to as much as 5:1.

The hyperglycemia causes osmotic diuresis leading to depletion of intravascular volume. As this progresses, impaired renal blood flow reduces the kidney's ability to excrete glucose, and hyperosmolality worsens. Severe hyperosmolality (>330 mOsm/kg) correlates closely with central nervous system depression and coma.

In a similar manner, impaired renal excretion of hydrogen ions aggravates the metabolic acidosis that occurs as a result of the accumulation of the ketoacids, β -hydroxybutyrate, and acetoacetate.

TABLE 17–20 Summary of some laboratory abnormalities in patients with coma directly attributable to diabetes or its treatment.

	Urine			Plasma		
	Glucose	Acetone	Glucose	Bicarbonate	Acetone	Osmolality
Diabetic ketoacidosis	++ to ++++	++++	High	Low	++++	+++
Hyperglycemic nonketotic coma	++ to ++++	0 or + ^a	High	Normal or slightly low ^b	0	++++
Hypoglycemia	0 ^c	0 or +	Low	Normal	0	Normal
Lactic acidosis	0 to +	0 or +	Normal, low, or high	Low	0 or +	Normal

^aA small degree of ketonuria may be present if the patient is severely stressed or has not been eating because of illness.

^bA patient may be acidotic if there is severe volume depletion with cardiovascular collapse or if sepsis is present.

^cLeftover urine in bladder might still contain sugar from earlier hyperglycemia.

The accumulation of ketones may cause vomiting, which exacerbates the intravascular volume depletion. In addition, prolonged acidosis can compromise cardiac output and reduce vascular tone. The result may be severe cardiovascular collapse with generation of lactic acid, which then adds to the already existent metabolic acidosis.

Clinical Features

A. Symptoms and signs The appearance of diabetic ketoacidosis is usually preceded by a day or more of polyuria and polydipsia associated with marked fatigue, nausea, and vomiting. Eventually, mental stupor ensues and can progress to frank coma. On physical examination, evidence of dehydration in a stuporous patient with rapid and deep respirations and the *fruity* breath odor of acetone strongly suggest the diagnosis. Postural hypotension with tachycardia indicates profound dehydration and salt depletion. Abdominal pain and even tenderness may be present in the absence of abdominal disease, and mild hypothermia is usually present.

B. Laboratory findings Typically, the patient with moderately severe diabetic ketoacidosis has a plasma glucose of 350 to 900 mg/dL (19.4–50 mmol/L), serum ketones are positive at a dilution of 1:8 or greater, hyperkalemia of 5 to 8 mEq/L, slight hyponatremia of approximately 130 mEq/L, hyperphosphatemia of 6 to 7 mg/dL, and an elevated blood urea nitrogen and creatinine. Acidosis may be severe (pH ranging from 6.9–7.2 with a bicarbonate concentration ranging from 5–15 mEq/L); pCO₂ is low (15–20 mm Hg) secondary to hyperventilation.

The fluid depletion is typically about 100 mL/kg. The hyperkalemia occurs despite total body potassium depletion, because of the shift of potassium from the intracellular to extracellular spaces in systemic acidosis. The average total body potassium deficit resulting from osmotic diuresis, acidosis, and gastrointestinal losses is about 3 to 5 mEq/kg body weight. Similarly despite the elevated serum phosphate, total body phosphate is generally depleted. Serum sodium is generally reduced, due to loss of sodium ions by polyuria and vomiting (7–10 mEq/kg), and because severe hyperglycemia shifts intracellular water into the interstitial compartment (for every 100 mg/dL of plasma glucose above normal, serum sodium decreases by 1.6 mEq/L). Serum osmolality can be directly measured by standard tests of freezing point depression or can be estimated by calculating the molarity of sodium, chloride, and glucose in the serum. A convenient formula for estimating effective serum osmolality is:

$$\text{mOsm/kg} = 2[\text{measured Na}^+] + \frac{\text{Glucose (mg/dL)}}{18}$$

The effective serum osmolality in humans is generally between 280 and 300 mOsm/kg. These calculated estimates are usually 10 to 20 mOsm/kg lower than values recorded by standard cryoscopic techniques. Central nervous depression or coma occurs when the effective serum osmolality exceeds 320 to 330 mOsm/L.

Blood urea nitrogen and serum creatinine are invariably elevated because of dehydration. Urea exerts an effect on freezing point depression as measured in the laboratory, but it is freely permeable across cell membranes and therefore not included in calculations of effective serum osmolality. Serum creatinine may also be falsely elevated due to interference from acetoacetate with some automated creatinine assays. However, most laboratories can correct for these interfering chromogens by using a more specific method, if asked to do so.

The nitroprusside reagents (Acetest and Ketostix) used for the bedside assessment of ketoacidemia and ketoaciduria measure only acetoacetate and its by-product, acetone. The sensitivity of these reagents for acetone, however, is quite poor, requiring over 10 mmol/L, which is seldom reached in the plasma of ketoacidotic subjects—although this detectable concentration is readily achieved in urine. Thus, in the plasma of ketotic patients, only acetoacetate is measured by these reagents. The more prevalent β-hydroxybutyrate has no ketone group and is therefore not detected by the conventional nitroprusside tests. This takes on special importance in the presence of circulatory collapse during diabetic ketoacidosis, wherein an increase in lactic acid can shift the redox state to increase β-hydroxybutyrate at the expense of the readily detectable acetoacetate. Bedside diagnostic reagents would then be unreliable, suggesting no ketonemia in cases where β-hydroxybutyrate is a major factor in producing the acidosis. Under these circumstances, β-hydroxybutyrate can be directly measured at the bedside using the Precision Xtra meter (Abbott Diagnostics). Many clinical laboratories now offer β-hydroxybutyrate measurement.

In about 90% of cases, serum amylase is elevated. However, this often represents salivary as well as pancreatic amylase and correlates poorly with symptoms of pancreatitis, such as pain and vomiting. Therefore, in patients with diabetic ketoacidosis, an elevated serum amylase does not justify a diagnosis of acute pancreatitis; serum lipase may be useful if the diagnosis of pancreatitis is being seriously considered.

Treatment

Patients with mild DKA are alert and have pH between 7.25 and 7.30; those with moderate DKA have pH between 7.0 and 7.24 and are alert or slightly drowsy; and those with severe DKA are stuporous and have pH <7.0. Those with mild DKA can be treated in the emergency room, but those with moderate or severe DKA require admission to the intensive care unit or step-down unit.

The therapeutic goals are to restore plasma volume and tissue perfusion; reduce blood glucose and osmolality toward normal; correct acidosis; replenish electrolyte losses; and identify and treat precipitating factors. Gastric intubation is recommended in the comatose patient to prevent vomiting and aspiration that may occur as a result of gastric atony, a common complication of diabetic ketoacidosis. In patients with preexisting cardiac or renal failure or those in severe cardiovascular collapse, a central venous pressure catheter or a Swan-Ganz catheter should be inserted to evaluate the degree of hypovolemia and to monitor subsequent fluid administration.

Plasma glucose should be recorded hourly and electrolytes and pH at least every 2 to 3 hours during the initial treatment period. A bedside glucose meter should be used to titrate the insulin therapy.

- 1. Fluid replacement.** In most adult patients, the fluid deficit is 4 to 5 L. Once the diagnosis of diabetic ketoacidosis is established in the emergency department, administration of at least 2 L of isotonic saline (0.9% saline solution) in an adult patient in the first 2 to 3 hours is necessary to help restore plasma volume and stabilize blood pressure while acutely reducing the hyperosmolar state. In addition, by improving renal plasma flow, fluid replacement also restores the renal capacity to excrete hydrogen ions, thereby ameliorating the acidosis as well. After the first 2 L of fluid have been given, the fluid should be changed to 0.45% saline solution given at a rate of 300 to 400 mL/h, because water loss exceeds sodium loss in uncontrolled diabetes with osmotic diuresis. Failure to give sufficient volume replacement (at least 3–4 L in 8 hours) to restore normal perfusion is one of the most serious therapeutic shortcomings affecting satisfactory recovery. In the same way, excessive fluid replacement (>5 L in 8 hours) may contribute to acute respiratory distress syndrome or cerebral edema. When blood glucose falls to approximately 250 mg/dL, the fluids should be changed to a 5% glucose solution to maintain plasma glucose in the range of 250 to 300 mg/dL. This prevents the development of hypoglycemia and also reduces the likelihood of cerebral edema, which may result from a too rapid decline of blood glucose.
- 2. Insulin.** Immediately after the initiation of fluid replacement, a rapid bolus of 0.15 U of regular insulin per kilogram of body weight should be given intravenously to prime the tissue insulin receptors. This inhibits both gluconeogenesis and ketogenesis while promoting utilization of glucose and keto acids. Following the initial bolus, an insulin infusion is initiated at a rate of 0.1 U/kg/h. When a continuous infusion of insulin is used, 25 U of regular human insulin should be placed in 250 mL of isotonic saline and the first 50 mL of solution flushed through to saturate the tubing before connecting it to the intravenous line. The insulin infusion should be piggy-backed into the fluid line so that the rate of fluid replacement can be changed without altering the insulin delivery rate. If the plasma glucose level fails to fall at least 10% in the first hour, a repeat loading dose is recommended. Rarely, a patient with insulin resistance is encountered; this requires doubling the insulin dose every 2 to 4 hours if severe hyperglycemia does not improve after the first two doses of insulin and fluid replacement. The insulin dose should be adjusted with the goal of lowering the glucose concentration by about 50 to 70 mg/dL/h. If clinical circumstances prevent use of insulin infusion, then the insulin can be given intramuscularly. An initial 0.15 U/kg of regular insulin is given intravenously, and at the same time, the same size dose is given intramuscularly. Subsequently, regular insulin is given intramuscularly hourly at a dose of 0.1 U/kg until the blood glucose falls to around 250 mg/dL, when the insulin can be given subcutaneously. Insulin therapy, either as a continuous infusion or as injections given every 1 to 2 hours, should be continued until arterial pH has normalized.
- 3. Potassium.** Total body potassium loss from polyuria and vomiting may be as high as 200 mEq. However, because of shifts of potassium from cells into the extracellular space as a consequence of acidosis, serum potassium is usually normal to slightly elevated prior to institution of treatment. As the

acidosis is corrected, potassium flows back into the cells, and hypokalemia can develop if potassium replacement is not instituted. If the patient is not uremic and has an adequate urine output, potassium chloride in doses of 10 to 30 mEq/h should be infused during the second and third hours after beginning therapy. Replacement should be started sooner, if the initial serum potassium is inappropriately normal or low, and should be delayed, if serum potassium fails to respond to initial therapy and remains above 5 mEq/L, as in cases of renal insufficiency. Cooperative patients with only mild ketoacidosis may receive part or all of their potassium replacement orally.

An electrocardiogram can be of help in monitoring the patient's potassium status: high peaked T waves are a sign of hyperkalemia, and flattened T waves with U waves are a sign of hypokalemia.

Foods high in potassium content should be prescribed when the patient has recovered sufficiently to take food orally. Tomato juice has 14 mEq of potassium per 240 mL, and a medium-sized banana has about 10 mEq.

- 4. Sodium bicarbonate.** The use of sodium bicarbonate in management of diabetic ketoacidosis has been questioned because clinical benefit was not demonstrated in one prospective randomized trial and because of the following potentially harmful consequences: (1) development of hypokalemia from rapid shift of potassium into cells if the acidosis is overcorrected, (2) tissue anoxia from reduced dissociation of oxygen from hemoglobin when acidosis is rapidly reversed (leftward shift of the oxygen dissociation curve), and (3) cerebral acidosis resulting from lowering of cerebrospinal fluid pH. It must be emphasized, however, that these considerations are less important when severe acidosis exists. It is therefore recommended that bicarbonate be administered to diabetic patients in ketoacidosis if the arterial blood pH is 7.0 or less with careful monitoring to prevent overcorrection.

One to two ampules of sodium bicarbonate (one ampule contains 44 mEq/50 mL) should be added to 1 L of 0.45% saline. (**Note:** Addition of sodium bicarbonate to 0.9% saline would produce a markedly hypertonic solution that could aggravate the hyperosmolar state already present.) This should be administered rapidly (over the first hour). It can be repeated until the arterial pH reaches 7.1, but *it should not be given if the pH is 7.1 or greater*, because additional bicarbonate increases the risk of rebound metabolic alkalosis as ketones are metabolized. Alkalosis shifts potassium from serum into cells, which can precipitate a fatal cardiac arrhythmia. As noted earlier, serious consideration should be given to placement of a central venous catheter when administering fluids to severely ill patients with cardiovascular compromise.

- 5. Phosphate.** Phosphate replacement is seldom required in treating diabetic ketoacidosis. However, if severe hypophosphatemia of less than 1 mg/dL (<0.35 mmol/L) develops during insulin therapy, a small amount of phosphate can be replaced per hour as the potassium salt. Correction of hypophosphatemia helps restore the buffering capacity of the plasma, thereby facilitating renal excretion of hydrogen. It also corrects the impaired oxygen dissociation from hemoglobin by regenerating 2,3-diphosphoglycerate. However, three randomized studies in which phosphate was replaced in only half of a group of patients with diabetic ketoacidosis did not show any apparent clinical benefit from phosphate administration. Moreover, attempts to use potassium phosphate as the sole means of replacing potassium have led to a number of reported cases of severe hypocalcemia with tetany. To minimize the risk

of inducing tetany from too rapid replacement of phosphate, the average deficit of 40 to 50 mmol of phosphate should be replaced intravenously at a rate *no greater than 3 to 4 mmol/h* in a 60- to 70-kg person. A stock solution (Abbott) provides a mixture of 1.12 g KH₂PO₄ and 1.18 g K₂HPO₄ in a 5-mL single-dose vial (this equals 22 mmol of potassium and 15 mmol of phosphate). One-half of this vial (2.5 mL) should be added to 1 L of either 0.45% saline or 5% dextrose in water. Two liters of this solution, infused at a rate of 400 mL/h, corrects the phosphate deficit at the optimal rate of 3 mmol/h and provides 4.4 mEq of potassium per hour. Additional potassium should be administered as potassium chloride to provide a total of 10 to 30 mEq of potassium per hour, as noted earlier. If the serum phosphate remains below 2.5 mg/dL after this infusion, a repeat 5-hour infusion can be given.

- 6. Hyperchloremic acidosis during therapy.** Because of the considerable loss of keto acids in the urine during the initial phase of therapy, substrate for subsequent regeneration of bicarbonate is lost, and correction of the total bicarbonate deficit is hampered. A portion of the bicarbonate deficit is replaced with chloride ions infused in large amounts as saline to correct the dehydration. In most patients, as the ketoacidosis clears during insulin replacement, a hyperchloremic, low-bicarbonate pattern emerges with a normal anion gap. This is a relatively benign condition that reverses itself over the subsequent 12 to 24 hours once intravenous saline is no longer being administered.

TRANSITION TO SUBCUTANEOUS INSULIN REGIMEN

Once the diabetic ketoacidosis is controlled and the patient is awake and able to eat, subcutaneous insulin therapy can be initiated. Initially, the patient may still have significant tissue insulin resistance and may require a total daily insulin dose of ~0.6 U/kg. Half of the total daily dose can be given as a long-acting basal insulin and the other half as short-acting insulin premeals. The patient should get injection of the basal insulin and a dose of the rapid-acting insulin analog with the first meal and the insulin infusion discontinued an hour later. The overlap of the subcutaneous insulin action and insulin infusion is necessary to prevent relapse of diabetic ketoacidosis. The increased tissue insulin resistance is only present for a few days at most and as the patient improves the doses of both basal and bolus insulins should be reduced to avoid hypoglycemia. In fact, a patient with new diagnosis of type 1 diabetes who still has significant β cell function may not require any basal insulin and only very low doses of rapid-acting insulin analogs before meals.

Complications and Prognosis

Low-dose insulin infusion and fluid and electrolyte replacement combined with careful monitoring of patients' clinical and laboratory responses to therapy have dramatically reduced the mortality rates of diabetic ketoacidosis to less than 5%. However, this complication remains a significant risk in the aged who have mortality rates over 20% and in patients in profound coma in whom treatment has been delayed. Acute myocardial infarction and infarction of the bowel following prolonged hypotension worsen the

outlook. Prior kidney dysfunction worsens prognosis because the kidney plays a key role in compensating for pH and electrolyte abnormalities. Symptomatic cerebral edema occurs primarily in the pediatric population. Risk factors for development include severe baseline acidosis, rapid correction of hyperglycemia, and excess volume administration in the first 4 hours. Onset of headache or deterioration in mental status during treatment should lead to consideration of this complication. Intravenous mannitol at a dosage of 1 to 2 g/kg given over 15 minutes is the mainstay of therapy. Excess crystalloid infusion can precipitate pulmonary edema. Acute respiratory distress syndrome is a rare complication of treatment for DKA.

Disposition

After recovery and stabilization, patients should receive intensive detailed instructions about how to avoid this potentially disastrous complication of diabetes mellitus. They should be taught to recognize the early symptoms and signs of ketoacidosis.

Urine ketones or capillary blood β -hydroxybutyrate should be measured in patients with signs of infection or in those using an insulin pump when capillary blood glucose is unexpectedly and persistently high. When heavy ketonuria and glycosuria persist on several successive examinations, supplemental regular insulin should be administered, and liquid foods such as lightly salted tomato juice and broth should be ingested to replenish fluids and electrolytes. Patients should be instructed to contact the physician if ketonuria persists and, especially, if vomiting develops, or if appropriate adjustment of the infusion rate on an insulin pump does not correct the hyperglycemia and ketonuria. Table 17–21 summarizes the guidelines for patients regarding ketone testing and what to do with the results. In adolescents, recurrent episodes of severe diabetic ketoacidosis often indicate poor compliance with the insulin regimen, and these patients should receive intensive family counseling.

2. HYPERGLYCEMIC, HYPEROSMOLAR STATE

This form of hyperglycemic coma is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence

TABLE 17–21 Guidelines for treatment of ketones in patients with type 1 diabetes.

Check ketones if blood glucose persistently over 250 mg/dL or if nauseated or vomiting	
Blood ketones <1.5 mmol/L or urine ketones absent or small	Blood ketones >1.5 or urine ketones moderate or large
Drink plenty of fluids	Call medical team for advise or go to urgent care or emergency room
Give fast-acting insulin by syringe Monitor glucose levels	Drink plenty of fluids Give fast-acting insulin by syringe Monitor ketone levels

Note: Blood ketones <0.6 mmol/L are normal.

of significant ketosis. It occurs in patients with mild or occult diabetes and patients are typically middle-aged or elderly. Lethargy and confusion develop as serum osmolality exceeds 300 mOsm/kg, and coma can occur if osmolality exceeds 330 mOsm/kg. Underlying renal insufficiency or congestive heart failure is common, and the presence of either worsens the prognosis. A precipitating event such as pneumonia, cerebrovascular accident, myocardial infarction, burns, or recent operation can often be identified. Certain drugs, such as phenytoin, diazoxide, glucocorticoids, and thiazide diuretics, have been implicated in its development, as have procedures associated with glucose loading such as peritoneal dialysis.

Pathogenesis

A partial or relative insulin deficiency may initiate the syndrome by reducing glucose utilization by muscle, fat, and liver, while promoting hyperglucagonemia and increasing hepatic glucose output. The result is hyperglycemia that leads to glycosuria and osmotic diuresis with obligatory water loss. The presence of even small amounts of insulin is believed to prevent the development of ketosis by inhibiting lipolysis in the adipose stores. Therefore, even though a low insulin-glucagon ratio promotes ketogenesis in the liver, the limited availability of precursor free fatty acids from the periphery restricts the rate at which ketones are formed. If a patient is unable to maintain adequate fluid intake because of an associated acute or chronic illness or has suffered excessive fluid loss (eg, from burns or therapy with diuretics), marked dehydration results. As plasma volume contracts, renal insufficiency develops; this, then, limits renal glucose excretion and contributes markedly to the rise in serum glucose and osmolality. As serum osmolality exceeds 320 to 330 mOsm/kg, water is drawn out of cerebral neurons, resulting in mental obtundation and coma.

Clinical Features

A. Symptoms and signs The onset of the hyperglycemic, hyperosmolar, nonketotic state may be insidious, preceded for days or weeks by symptoms of weakness, polyuria, and polydipsia. A history of reduced fluid intake is common, whether due to inappropriate absence of thirst, gastrointestinal upset, or, in the case of elderly or bedridden patients, lack of access to water. A history of ingestion of large quantities of glucose-containing fluids, such as soft drinks or orange juice, can occasionally be obtained; these patients are usually less hyperosmolar than those in whom fluid intake was restricted. The absence of toxic features of ketoacidosis may retard recognition of the syndrome and thus delay institution of therapy until dehydration is profound. Because of this delay in diagnosis, the hyperglycemia, hyperosmolarity, and dehydration in hyperglycemic, hyperosmolar, nonketotic coma is often more severe than in diabetic ketoacidosis.

Physical examination reveals the presence of profound dehydration (orthostatic fall in blood pressure and rise in pulse, supine tachycardia, or even frank shock, dry mucous membranes, decreased skin turgor). The patient may be lethargic, confused, or comatose. Kussmaul respirations are absent unless the precipitating event for

the hyperosmolar state has also led to the development of metabolic acidosis (eg, sepsis or myocardial infarction with shock).

B. Laboratory findings Severe hyperglycemia is present, with blood glucose values ranging from 800 to as high as 2400 mg/dL (44.4–133.2 mmol/L). In mild cases, where dehydration is less severe, dilutional hyponatremia as well as urinary sodium losses may reduce serum sodium to about 120 to 125 mEq/L—this protects, to some extent, against extreme hyperosmolality. Once dehydration progresses further, however, serum sodium can exceed 140 mEq/L, producing serum osmolalities of 330 to 440 mOsm/kg (normal, 280 to 295 mOsm/kg; see the section Diabetic Ketoacidosis for a convenient method for estimating serum osmolality). Ketosis is usually absent or mild; however, a small degree of ketonuria may be present if the patient has not been eating because of illness. Acidosis is not a part of the hyperglycemic, hyperosmolar state, but it may be present (often lactic acidosis) because of other acute underlying conditions (eg, sepsis, acute renal failure, myocardial infarction). Prerenal azotemia is the rule with blood urea nitrogen frequently over 100 mg/dL.

The physician must initiate a careful search for the event that precipitated the episode of hyperglycemic, hyperosmolar state if it is not obvious after the initial history and physical examination. Chest x-rays and cultures of blood, urine, and other body fluids should be obtained to look for occult sources of sepsis. Cardiac enzymes and serial electrocardiograms can be ordered to look for evidence of silent myocardial infarction.

Treatment

There are some differences in fluid, insulin, and electrolyte replacement in this disorder, as compared with diabetic ketoacidosis. However, in common with the treatment of ketoacidotic patients, careful monitoring of the patient's clinical and laboratory response to therapy is essential.

1. Fluid replacement. The fluid deficit may be as much as 100 to 200 mL/kg or about 9 L. If circulatory collapse is present, fluid therapy should be initiated with isotonic saline. In all other cases, initial replacement with hypotonic (usually 0.45%) saline is preferable, because these patients are hyperosmolar with considerable loss of body water and excess solute in the vascular compartment. As much as 4 to 6 L of fluid may be required in the first 8 to 10 hours. Careful monitoring of fluid quantity and type, urine output, blood pressure, and pulse is essential. Placement of a central venous pressure catheter should be strongly considered to guide replacement of fluid, especially if the patient is elderly or has underlying renal or cardiac disease. Because insulin therapy decreases plasma glucose and therefore serum osmolality, a change to isotonic saline may be necessary at some time during treatment. Once blood glucose reaches 250 mg/dL, 5% dextrose in 0.45% or 0.9% saline solution should be substituted for the sugar-free fluids. When consciousness returns, oral fluids should be encouraged.

2. Electrolyte replacement. Hyperkalemia is less marked, and much less potassium is lost in the urine during the osmotic diuresis of hyperglycemic, hyperosmolar, nonketotic coma than in diabetic ketoacidosis. There is, therefore, less severe total potassium depletion, and less potassium replacement is

needed to restore potassium stores to normal. However, because the initial serum potassium usually is not elevated and because it declines rapidly as insulin therapy allows glucose and potassium to enter cells, it is recommended that potassium replacement be initiated earlier than in ketotic patients: 10 mEq of potassium chloride can be added to the *initial* liter of fluid administered if the initial serum potassium is not elevated and if the patient is making urine. When serum phosphate falls below 1 mg/dL during insulin therapy, phosphate replacement can be given intravenously with the same precautions as those outlined for ketoacidotic patients (see earlier). If the patient is awake and cooperative, part or all of the potassium and phosphate replacement can be given orally.

3. Insulin therapy. In general, less insulin is required to reduce the hyperglycemia of nonketotic patients than is the case for patients in diabetic ketoacidosis. In fact, fluid replacement alone can decrease glucose levels considerably. An initial insulin bolus of 0.15 U/kg is followed by an insulin infusion rate of 0.1 U/kg/h titrated to lower blood glucose by 50 to 70 mg/dL/h. Once the patient has stabilized and the blood glucose falls to around 250 mg/dL, insulin can be given subcutaneously.

Complications and Prognosis

The severe dehydration and low output state may predispose the patient to complications such as myocardial infarction, stroke, pulmonary embolism, mesenteric vein thrombosis, and disseminated intravascular coagulation. Fluid resuscitation remains the primary approach to the prevention of these complications. Low-dose heparin prophylaxis is reasonable but benefits of routine anticoagulation remain doubtful. Rhabdomyolysis is a recognized complication of the hyperosmolar state, and it should be looked for and treated.

The overall mortality rate of hyperglycemic, hyperosmolar, nonketotic coma is over 10 times that of diabetic ketoacidosis, chiefly because of its higher incidence in older patients, who may have compromised cardiovascular systems or associated major illnesses. When patients are matched for age, the prognoses of these two forms of hyperosmolar coma are reasonably comparable.

Disposition

After the patient is stabilized, the appropriate form of long-term management of the diabetes must be determined. Insulin treatment should be continued for a few weeks, but the patients usually recover sufficient endogenous insulin secretion to make a trial of diet or diet plus oral agents worthwhile. When the episode occurs in a patient who has known diabetes, then education of the patient and caregivers should be instituted. They should be taught how to recognize situations (gastrointestinal upset, infection) that predispose to recurrence of hyperglycemic, hyperosmolar state as well as detailed information on how to prevent the escalating dehydration (small sips of sugar-free liquids, increase in usual hypoglycemic therapy, or early contact with the physician) that culminates in hyperosmolar coma.

3. LACTIC ACIDOSIS

When severely ill diabetic patients present with profound acidosis and an anion gap over 15 mEq/L but relatively low or undetectable

levels of keto acids in plasma, the presence of excessive plasma lactate (>5 mmol/L) should be considered, especially if other causes of acidosis such as uremia are not present.

Pathogenesis

Lactic acid is the end product of the anaerobic metabolism of glucose. Normally, the principal sources of this acid are the erythrocytes (which lack the enzymes for aerobic oxidation), skeletal muscle, skin, and brain. The chief pathway for removal of lactic acid is by hepatic (and to some degree renal) uptake for conversion first to pyruvate and eventually back to glucose, a process that requires oxygen. Lactic acidosis occurs when excess lactic acid accumulates in the blood. This can be the result of overproduction (tissue hypoxia), deficient removal (hepatic failure), or both (circulatory collapse). Lactic acidosis is not uncommon in any severely ill patient suffering from cardiac decompensation, respiratory or hepatic failure, septicemia, or infarction of the bowel or extremities. Type A lactic acidosis is associated with tissue hypoxia from hypovolemia or endotoxic shock and need not be associated with hyperglycemia. Type B lactic acidosis is defined as that which occurs in the absence of clinical evidence for tissue hypoxia and is associated with diabetes per se or with biguanide therapy.

With the discontinuance of phenformin therapy in the United States, lactic acidosis in patients with diabetes mellitus has become uncommon, but it still must be considered in the acidotic diabetic patient if the patient is seriously ill, and especially if the patient is receiving metformin therapy as well. Most cases of metformin-associated lactic acidosis occur in patients in whom there were contraindications to the use of metformin, in particular renal failure.

Clinical Features

A. Symptoms and signs The main clinical features of lactic acidosis are marked hyperventilation and mental confusion, which may progress to stupor or coma. When lactic acidosis is secondary to tissue hypoxia or vascular collapse, the clinical presentation is variable, reflecting that of the prevailing catastrophic illness. In the rare instance of idiopathic or spontaneous lactic acidosis, the onset is rapid (usually over a few hours), the cardiopulmonary status is stable, and mentation may be relatively normal.

B. Laboratory findings Plasma glucose can be low, normal, or high in diabetic patients with lactic acidosis, but usually it is moderately elevated. Plasma bicarbonate and arterial pH are quite low. An anion gap is present (calculated by subtracting the sum of the plasma bicarbonate and chloride from the plasma sodium; normal is 12–15 mEq/L). Ketones are usually absent from plasma, but small amounts may be present in urine if the patient has not been eating recently. Other causes of anion gap metabolic acidosis should be excluded—for example, uremia, diabetic or alcoholic ketoacidosis, and salicylate, methanol, ethylene glycol, or paraldehyde intoxication. In the absence of azotemia, hyperphosphatemia may be a clue to the presence of lactic acidosis.