34 Acute Metabolic Complications of Diabetes: Diabetic Ketoacidosis and Hyperosmolar Hyperglycemia

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Keypoints

Diabetic ketoacidosis

- Lack of insulin is the culprit in diabetic ketoacidosis.
- The most common precipitating cause is infection.
- The classic signs include polyuria and polydipsia, rapid weight loss, weakness, Kussmaul respiration, drowsiness and, rarely, coma.
- The cornerstones of treatment are rehydration, IV insulin and potassium supplementation.
- Intravenous insulin administration should continue until the acidosis is normalized (i.e. not merely until euglycemia is achieved).

Hyperosmolar non-ketotic hyperglycemia

- This is characterized by hyperosmolality with progressive hyperglycemia of >35–40 mmol/L and an effective serum osmolality of >320 mOsm/kg.
- It typically affects elderly patients with type 2 diabetes.
- The most common precipitating causes are infection and cardiovascular disease.
- Treatment involves aggressive rehydration and IV insulin.

Introduction

Both diabetic ketoacidosis (DKA) and hyperosmolar non-ketotic hyperglycemia (HH) are caused by a lack of insulin leading to unrestricted flux of stored lipid, carbohydrate and amino acid nutrients into the blood. These conditions are both acute and life-threatening, and represent the ultimate metabolic consequences of deranged type 1 (T1DM) and type 2 diabetes mellitus (T2DM), respectively [1–3]. The hallmark of DKA is a high-anion-gap metabolic acidosis caused by a rapidly progressive excess of ketoacids (3-hydroxybutyrate and acetoacetate – "ketone bodies") while severe hyperosmolarity caused by hyperglycemia is the most notable feature of HH. The distinction is not always obvious on clinical grounds; patients with DKA may be very hyperosmolar and ketone body levels are in general somewhat elevated in HH. Although the clinical picture may vary considerably depending on co-morbidities, differential diagnosis seldom poses any major problem and in the rare cases in which distinction remains difficult, treatment generally follows the same principles, regardless of whether ketosis or hyperglycemia is the most urgent clinical challenge.

Mortality rates have been steadily declining over the past few years [4], but remain close to 5% for DKA and 10–15% for HH [2,5]. The decline in mortality may be a consequence of lower incidence of DKA and HH, earlier diagnosis, improved treatment or, more plausibly, all of these effects combined. Improved education schedules and self-monitoring (e.g. blood ketone testing), organization of specialized diabetes clinics and the use of standardized low-dose insulin regimens have also contributed to this favorable trend [2,6].

Diabetic ketoacidosis

Definitions

Diabetic ketoacidosis is the most common, serious and demanding medical emergency within the fields of diabetology and endocrinology. There is no generally accepted definition of DKA and, in particular, very mild cases may be difficult to diagnose. At a minimum, it is reasonable to require that pH is below the normal range and that the levels of ketoacids (ketone bodies) in the blood or urine are markedly elevated. As outlined in Table 34.1, there is a continuous deterioration from clinically insignificant "stress" ketosis to full-blown severe ketoacidosis. In the US population,

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein.

Table 34.1 Classification of clinical pictures and diagnostic criteria. Adapted from Standards of Medical Care in Diabetes – 2004/2006 position statement. *Diabetes Care* 2004; **27**:S94–S101, with permission from the American Diabetes Association.

	Stress ketosis	Compensated DKA	Diabetic ketoacidosis			Hyperosmolar hyperglycemia
			Mild	Moderate	Severe	
Plasma glucose	Variable	Generally increased	Generally increased	Generally increased	Generally increased	>35–40 mmol/L
Arterial pH	Normal	Normal	Decreased >7.25	7.0–7.25	<7.0	Generally normal
Serum bicarbonate	Normal	Marginally decreased	15–18 mmol/L	10–15 mmol/L	<10 mmol/L	>15 mmol/L
Urine ketones	Increased	Increased	Increased	Increased	Increased	Normal/marginally increased
Blood ketones	Increased	Increased	Increased	Increased	Increased	Normal/marginally increased
Anion gap*	Normal/marginally increased	Marginally increased	>10	>12	>12	Variable
Mental status	Normal	Normal	Normal	Normal/drowsy	Drowsy–coma	Drowsy–coma

DKA, diabetic ketoacidosis.
* Anion gap can be calculated as: $[Na^+]-([Cl^-]+[HCO^{-3}])$.

it has been estimated that 2–8% of hospital admissions in children with diabetes are a result of DKA and that the annual incidence rate of DKA in children is around 5 per 1000 patients [1].

Pathogenesis and pathophysiology

Insulin deficiency

DKA is caused by insulin deficiency. Insulin deficiency may be relative (e.g. in the setting of severe infection) where normal amounts of insulin are insufficient, or absolute when insulin therapy is neglected. Lack of insulin leads to uncontrolled lipolysis and ketogenesis and increases plasma glucose. Although often disregarded it should also be borne in mind that insulin deficiency, most particularly when longstanding, causes increased breakdown of body protein, as evidenced by the extreme sarcopenia and cachexia of patients with T1DM prior to the insulin era. Excessive protein breakdown and ensuing release of ketogenic and gluconeogenic amino acids may contribute to ketosis and hyperglycemia.

Stress hormones and cytokines

At some stage insulin deficiency becomes coupled with excess of "counter-regulatory" or "stress" hormones and cytokines [7,8]. Release of stress hormones may in part be triggered by cytokines and in part by general stress, such as dehydration, hypotension and hypoperfusion. It has been shown that both endotoxin and tumor necrosis factor (TNF) mimics all metabolic responses to infection including hyperthermia and stress hormone release [9,10]. The traditional stress hormones include glucagon, epinephrine, growth hormone (GH) and cortisol, all of which have well-described metabolic actions. Glucagon and epinephrine have a rapid onset of action, whereas GH and cortisol act with a latency of hours.

Cytokine levels are elevated in DKA, even in the absence of infection. The metabolic actions of cytokines are in general not so well understood and it is possible that many of these actions are mediated by hypothalamo-pituitary activation and subsequent stress hormone release. Certain cytokines, such as TNF-α, may impair insulin sensitivity in peripheral tissues [11,12] and a vicious circle may thus be initiated with self-perpetual increments in blood glucose and cytokine levels. Insulin has anti-inflammatory properties in critically ill patients [13], and administration of exogenous insulin may in itself increase insulin sensitivity [14], conceivably to some extent by breaking this vicious circle but also because glucotoxicity and lipotoxicity wane.

Lipid metabolism

Contrary to popular belief, deranged lipid – not carbohydrate – metabolism is the main cause of DKA. In essence, DKA is brought about by uncontrolled lipolysis in adipose tissue and uncontrolled ketogenesis in liver.

Adipose tissue is present in regional depots such as subcutaneous upper and lower body and visceral fat [15]. Apart from these classic depots, fat is present in most other tissues (e.g. connective tissue, bone marrow, liver and muscle). The picture is further complicated by the fact that within each tissue fat is distributed in compartments. In muscle, for instance, fat is present intramyocellularly, intermyocellularly and intermuscularly. Under physiologic conditions, lipolysis is tightly controlled by lipases. Hormone-sensitive lipase and probably also adipose triglyceride lipase stimulate release of free fatty acids and glycerol into the circulation. This process is inhibited by insulin and low insulin levels increase lipolysis swiftly. The stress hormones, such as epinephrine, growth hormone and cortisol, stimulate lipolysis. It is plausible that dehydration per se also participates in the stimulation of lipolysis [16]. These events take place in the course of hours and may rapidly triple or quadruple blood concentrations of free fatty acids.

Ketogenesis occurs in the liver by oxidation of free fatty acids to ketoacids or ketone bodies (Figure 34.1). Ketone bodies, in

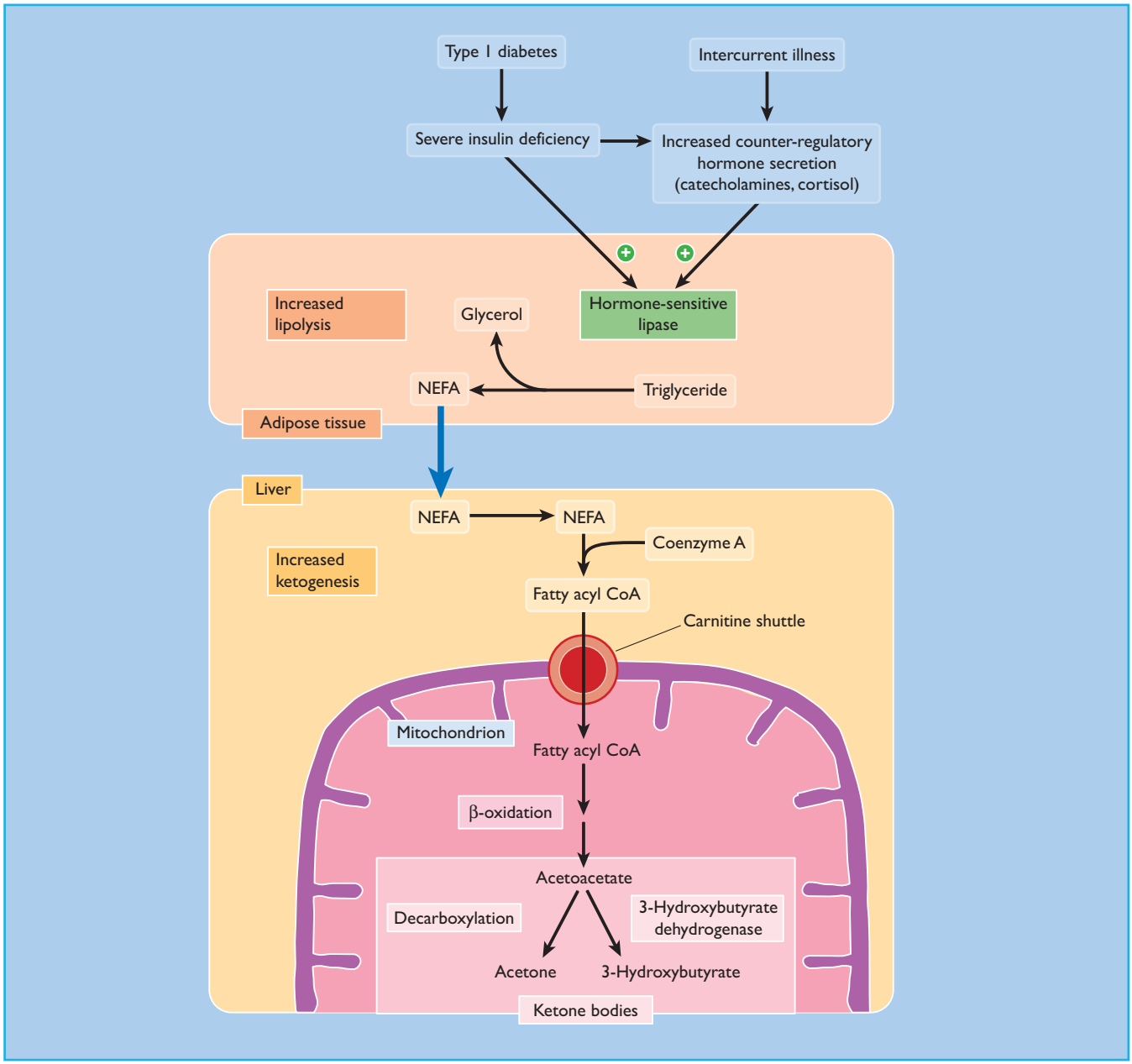

Figure 34.1 Mechanisms of ketogenesis. NEFA, non-esterified fatty acids.

particular 3-OH-butyrate, are phylogenetically ancient fuel compounds, which are present and prominent in very primitive species [17], suggesting that they have had an important role throughout evolution for the past 2–3 billion years. Physiologically, ketone bodies provide important fuel energy for the brain and other tissues under fasting, prolonged exercise and other conditions of fuel shortage. In DKA, ketogenesis becomes uncontrolled and circulating levels of ketone bodies rise rapidly and excessively. This occurs because of both increased supply of fatty acids to the liver and because low levels of insulin and high levels of glucagon in the liver promotes ketogenesis [18]. In normal individuals this unrestrained process is prevented by compensatory rises in insulin secretion, but this does not occur in those with T1DM.

Glucose metabolism

Hyperglycemia is usually present in DKA, but it is important to stress that DKA not infrequently presents with normal or modestly elevated glucose concentrations [19]. This may particularly be the case during caloric deprivation caused by gastrointestinal disease, for example. Hyperglycemia is caused by a combination of lack of insulin and an excess of stress hormones, leading to insulin resistance. In the liver this increases gluconeogenesis and hepatic glucose production. The kidney is unlikely to have any

significant role in the initial stages of DKA [20]. The ensuing high glucose levels generate a high flux state with increased peripheral glucose disposal, but the increased mass action of glucose is generally insufficient to compensate fully. Muscle glucose metabolism is characterized by insulin resistance because of high levels of stress hormones, high levels of free fatty acids and varying degrees of dehydration.

Precipitating factors

In patients with known diabetes, DKA is usually precipitated by a coexisting illness or by omission of insulin therapy. The most common factor is infection, ranging from trivial viral infections to full-blown septicemia. Other precipitating factors include cardiovascular events (myocardial infarction, stroke), gastrointestinal disease, inflammatory diseases, pancreatitis, trauma and major surgery, alcohol abuse and drugs, especially glucocorticoids. All of these factors induce insulin resistance because of the stress hormone responses. Furthermore, poor appetite and food deprivation will often lead the patient to take less insulin. In this context, gastrointestinal disease with nausea and vomiting pose a specific problem and it may be necessary to admit such patients to the hospital for intravenous glucose and insulin therapy. Diabetes ketoacidosis may be a presenting feature of new onset T1DM (see Chapter 19).

Psychologic factors also play an important part. Poor compliance is commonly seen in younger patients, patients with psychiatric illnesses and in minority groups who unfortunately may have a poor understanding of diabetes care principles for linguistic or cultural reasons.

Diagnosis and clinical presentation

DKA usually develops over a short period of time, generally in less than 24 hours. There may have been some antecedent days with general malaise and poor metabolic control. Depending on the degree of hyperglycemia, the history will include symptoms of polydipsia and polyuria (Table 34.2). Specific symptoms depend on the precipitating factors and other co-morbidities that might be present. Physical examination may reveal poor skin turgor, hyperventilation (Kussmaul respirations), hypotension, tachycardia and impairment of mental state. Many patients have infections but with normothermia or even hypothermia, caused by peripheral vasodilatation brought about by the acidemia.

Table 34.2 Common clinical features of diabetic ketoacidosis.

Polyuria, polydipsia
Rapid weight loss
Muscular weakness
Visual disturbance
Air hunger with Kussmaul respiration, dry lips
Abdominal pain, leg cramps
Nausea, vomiting
Confusion, drowsiness, coma

Prompt diagnosis and initial treatment rests on:

1 Careful clinical examination;
2 Determination of plasma glucose;
3 Measurement of ketones in blood or urine;
4 Measurement of plasma potassium and other electrolytes; and
5 Assessment of acidemia.

If glucose is high and blood or urine ketones are markedly elevated, DKA is likely and fluid and insulin therapy can usually be intiated, unless the patient is severely hypokalemic (<3.5 mmol/L). If potassium is very low, supplementation must be given prior to insulin therapy; however, rehydration should not be delayed while waiting for a potassium measurement.

The next diagnostic steps usually include arterial blood gas analysis, blood electrolytes (including anion gap), serum lactate (if there is doubt about the cause of the acidemia), complete blood cell count, biochemical assessment of liver and renal function, blood and urine cultures, myocardial biomarkers (if there is suspicion of a myocardial infarction), electrocardiogram (ECG) and chest X-ray. In this context it is advantageous that most modern gas analyzers also readily provide potassium concentrations. Another recent advantage is the advent of bedside ketone body monitors. Thus, it is now possible to have a quick and reliable measure of 3-hydroxybutyrate concentrations in blood, as opposed to unreliable measurements of acetoacetate in urine or the time-consuming conventional laboratory methods used in the past. The diagnostic criteria are shown in Table 34.1.

Despite potassium depletion, serum potassium is typically either normal or elevated because of water deficiency and an intracellular to extracellular shift caused by insulin deficiency and acidemia. Patients with potassium in the low range have a severe total body potassium deficiency and should receive vigorous replacement therapy guided by cardiac monitoring. Sodium concentrations can be normal or low, as a result of osmotic shifts. It can be calculated that for every 3 mmol/L rise in plasma glucose the plasma sodium falls by 1 mmol/L. Thus, there is often a real hypernatremia with sodium levels rising as the glucose is brought under control. A majority of patients will have a leukocytosis, which correlates with ketone body levels rather than with the presence of infection. There is also a water deficit of around 10% of body weight. Non-specific elevations of amylase and liver enzymes are also common.

Differential diagnoses include all other causes of acidosis. Note that many acute medical conditions induce a stress ketosis and may be associated with acidosis. DKA is a metabolic acidosis characterized by a high anion gap and varying degrees of respiratory compensation. Thus, it is crucial to obtain measures of ketone body concentrations and perform an arterial gas analysis. If there is a major discrepancy between the extent of the ketonemia and the acidemia then lactate measurements are warranted. Starvation ketosis and alcoholic ketoacidosis can usually be identified by clinical history. Other conditions causing metabolic acidosis include lactic acidosis and intoxication with salicylate, methanol, ethylene glycol (antifreeze) and paraldehyde. The clinical picture may be blurred whenever the acidosis is aggra-

vated by renal failure or respiratory failure. In addition, DKA may imitate other diseases. High levels of potassium may also cause ECG changes suggestive of myocardial infarction and elevation of myocardial enzymes and biomarkers may occur in the absence of a clinical myocardial infarction [21]. DKA may also mimic an acute abdomen, particularly in younger patients.

Management

Management and treatment of DKA rests on four pillars:

1. Fluid and electrolyte therapy;
2. IV insulin therapy;
3. Treatment of co-morbidities; and
4. Careful monitoring of the clinical course.

It is particularly important that treatment is initiated without delay and that the patient is monitored frequently and carefully, preferably in a highly specialized unit. Severe cases should be treated and monitored in an intensive care unit where possible. Useful algorithms for treatment are available from many sources including the American Diabetes Association. In general, the overall goal is a controlled, gradual correction of metabolic abnormalities and fluid and electrolyte deficiencies in the course of around 24 hours.

Treatment of DKA in children and young adolescents follows slightly different guidelines than those presented below (see Chapter 51) [22]. It is recommended that in children insulin is given continuously intravenously (0.1 IU/kg body weight/hour) after initiation of fluid and electrolyte therapy in order to minimize the risk of cerebral edema. Otherwise children are in general treated with weight reduced doses as indicated below.

Fluid/saline therapy

The first priority is to start to replace fluids. Water and sodium deficits typically are around 10% of body weight and 10 mmol/kg and isotonic saline (0.154 mmol/L; 0.9% NaCl) is given at a rate of approximately 15–20 mL/kg/hour or 1 L/hour initially, followed by 250 mL/hour after the first 2–3 hours depending on the state of dehydration. Depending on prevailing sodium concentrations and hydration, hypotonic saline may also be used, but this is rarely necessary. Urine production as well as cardiovascular, renal and mental performance should be monitored frequently.

Insulin

Lack of insulin is the culprit in DKA and insulin treatment is mandatory. Insulin therapy in adults is given by infusion of 0.1 IU/kg body weight/hour or more simply as 6 units/hour. An IV bolus of 0.15 IU/kg body weight (or 10 IU) of regular insulin can be given initially but is not really required, as most of the initial improvement in metabolic status is brought about by rehydration. Alternatively, a bolus of 0.15 IU/kg body weight (or 10 IU) may be given every hour or a 20 unit bolus IM followed by 6 units every hour. If the patient is very insulin resistant as assessed by daily insulin requirements, dosage can be increased and vice versa if the patient is insulin sensitive. Considering the short half-life of IV administered insulin, it is imperative that insulin is given at least every hour, regardless of the prevailing blood glucose.

Insulin therapy is adjusted based on hourly measurements of blood glucose and – if possible – blood ketones, with the overall aim being a gradual decline in both. The initial decline is to a large extent caused by rehydration and expansion of the extracellular volume. Repeated analysis of arterial blood gases may be indicated but only in those patients with very low pH values and/or poor clinical condition. Measurements of ketone levels in urine is in general unreliable in this phase; these methods measure acetoacetate, which is quantitatively of minor importance compared to 3-OH-butyrate and acetoacetate in urine may exhibit an paradoxical initial increase because of increasing blood concentrations (and low urine production), despite successful treatment. In particular, acetone is also measured by standard urine dipstick methods and may continue to be excreted for up to 48 hours after the onset of treatment as it is fat soluble and leaches out slowly during treatment.

When glucose concentrations are 10–15 mmol/L, glucose is given IV and/or orally to avoid hypoglycemia. It is usually possible to taper IV insulin treatment when 3-hydroxybutyrate concentrations are well below 3 mmol/L. Ten percent glucose should be used for IV replacement as this provides some extra anabolic substrate. If the patient is still dehydrated then the saline infusion should be continued.

Potassium, bicarbonate and phosphate

Potassium

Even though the body is potassium depleted, with a typical deficit of around 5 mmol/kg, initial potassium values are usually normal or elevated. Insulin therapy, rehydration and correction of acidosis all cause a decrease in serum potassium and 20–30 mmol potassium/hour may be administered once potassium levels are below 5.0 mmol/L, provided renal function is intact. Subsequent potassium administration is guided by frequent concentration measurements; adjuvant oral administration may be used in very mild cases of DKA. It is a frequent practical problem that there may be some delay before values are available from the laboratory; gas analyzers that provide instant bedside potassium concentrations greatly facilitate this process.

Bicarbonate

Bicarbonate use in DKA is a matter of controversy [23], but it is empirically recommended that 25–50 mmol sodium bicarbonate is given hourly for 1–2 hours if the pH is below 7.0.

Phosphate

Phosphate deficiency of around 1 mmol/kg is typically present in DKA, but there is no evidence that phosphate supplementation should be given routinely. In patients with severe hypophosphatemia and/or cardiac and skeletal or respiratory muscle weakness, 20–30 mmol potassium phosphate can be given hourly for 1–2 hours.

Co-morbidity

Coexisting diseases precipitate DKA and DKA precipitates coexisting disease. Most often, patients with DKA have infectious disease and signs of infection should be vigorously sought for and treatment should be instituted as appropriate. Other prominent co-morbidities include cardiovascular events (myocardial infarction, stroke, thrombophlebitis, pulmonary embolism), acute gastrointestinal disorders and a variety of intoxications.

Complications

Iatrogenic hypoglycemia and hypokalemia are common and preventable, provided there is access to rapid analysis of glucose and potassium and – not less important – a competent and experienced medical team. Another frequent complication is recurrence of DKA or unnecessary protraction of the course, typically caused by insufficient insulin therapy. Thrombotic events are also not uncommon although more often in HH than DKA.

Cerebral edema is a rare, but often fatal, complication preponderant in children and adolescents. The pathophysiology is poorly understood, but may relate to overly aggressive therapy, the use of hypotonic replacement fluids, local cerebral overhydration and abnormalities of vasogenic function [22]. Symptoms frequently develop 4–12 hours after initiation of therapy and include headache, altered mental status, specific neurologic deficits and signs of increased intracranial pressure. Treatment with mannitol or hypertonic saline may be beneficial in this condition.

In some patients, the high anion-gap ketoacidosis may be further complicated by the appearance of a non-anion-gap hyperchloremic acidosis during treatment with insulin and saline infusions [24]. This is because of loss of alkali in the form of ketoanions with sodium or potassium in the urine. This component often results in protracted acidosis, which can confuse clinical assessment. Some of these patients may benefit from bicarbonate therapy.

Prevention

Implementation of self-care and shared-care principles is crucial. Patients should learn about symptoms of DKA and be able to measure ketones in blood or urine when they feel ill or if their blood glucose is high. A common lapse is the omission or reduction of insulin during episodes with impaired well-being and poor appetite. Persistent ketosis should be treated with extra insulin, fluid and carbohydrate, when necessary. Furthermore, it is very important that the individual patient has ready, 24 hours/day access to diabetologic expertise, preferably in a specialized diabetes center.

Hyperosmolar hyperglycemia

Hyperosmolar hyperglycemia (HH) is generally the fulminant result of poorly treated T2DM or delayed diagnosis of previously unknown T2DM. HH is less frequent than DKA, but mortality is higher and remains close to 15% in many centers [2,25]. As implied, hyperosmolality is the primary clinical problem accompanied by hyperglycemia of >35–40 mmol/L and an effective serum osmolality of >320 mOsm/kg (Table 34.1). HH most often occurs in frail patients in combination with other potentially fatal conditions. Strict differentiation between DKA and HH can be difficult, because some degree of ketosis may be present in HH and because lactic acidosis, respiratory and renal failure may also be present. In practice this dilemma is mainly ornamental, because diagnostic and therapeutic efforts follow the same principles.

In line with DKA, HH is most often precipitated by infectious diseases or cardiovascular events and symptoms of hyperglycemia usually have been present for some days. Hyperglycemia is caused by a vicious cycle, in which relative insulin deficiency and high levels of stress hormones lead to increased endogenous glucose production and decreased peripheral glucose utilization; hyperglycemia in turn induces hyperosmolality and dehydration, which amplifies the stress hormone response and further impairs insulin secretion and vice versa.

At presentation, the patient's clinical condition is poor, with severe dehydration, poor skin turgor and often an altered level of consciousness (ranging from drowsiness to coma) and signs of hypovolemic shock. In general, the diagnostic procedures are similar to DKA. Typically, there will be a water deficit of 10–20% of body weight together with sodium, chloride and potassium deficits of 5–10 mmol/kg body weight.

Treatment of HH in general follows the same guidelines as for DKA, the main aim being a controlled correction of hyperglycemia, hyperosmolality and water and electrolyte deficits over 24 hours. Patients are generally more sensitive to insulin and an infusion of 0.1 IU/kg body weight/hour is more than adequate in most cases. Repeated hourly boluses of 0.15 IU/kg body weight (or 10 IU) may also be used. As with DKA, the dosage should be adjusted according to normal daily insulin needs and depending on the therapeutic response. Usually 1 L isotonic saline is infused in the first hour but after that slower rehydration is advisable. Hemodynamic performance should be monitored carefully and it should be borne in mind that many of the patients have pre- or coexisting cardiac disease. The use of a central venous pressure line is helpful. It should be noted that a significant proportion of HH patients are hypernatremic. In this case hypotonic saline can be used but more slowly. Potassium is administered along the same lines as with DKA and it is often prudent to monitor the patient in the intensive care unit.

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