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Diabetic Ketoacidosis: A Current Appraisal of Pathophysiology and Management

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Diabetic ketoacidosis (DKA) is a frequent abnormal metabolic entity seen in high-dependency units such as critical care units and in the emergency department. Having an understanding of its pathophysiology, a consequence of absent to low insulin levels, delineates the clinical presentation. Most clinical features are caused by hyperglycemia and acidosis, including weight loss. The newer management modalities are discussed that include the need for intensive laboratory workup, meticulous monitoring of the insulin, and fluid management. Among the complications, cerebral edema (CE) is the most dreaded, albeit with low incidence. The new insights into its pathophysiology and management are outlined, and a timeline for management of DKA is proposed.

Keywords: DKA; pathophysiology; cerebral edema; management; serum osmolality

Definition

The first clinical description of diabetic ketoacidosis (DKA) was provided by Dreschfeld in 1886.[1] It accounts for 8% to 29% of all hospital admissions with primary diagnosis of diabetes. Whereas the individual costs of hospitalization for DKA are calculated at $13 000, the annual expenditure is more than 1 billion dollars; however mortality resulting from DKA is showing a declining trend.[2]

DKA is a result of severe insulin deficiency or of insulin resistance with relative insulin deficiency. It is defined by an elevated serum glucose of >11 mmol/L; acidosis (venous pH < 7.30 or bicarbonate level of < 15 mmol/L); serum ketonemia (β-hydroxybutyrate > 300 μmol/L); and ketonemia, ketonuria, and glycosuria.[3,4] Also, euglycemic DKA has been reported in up to 18% of the cases.[5] DKA needs to be distinguished from the syndrome of a hyperglycemic, hyperosmolar nonketotic state, for there are important differences in their pathophysiology and management. The latter is defined as having a blood glucose level of >33 mmol/L, serum osmolality > 330 mosm/L, and pH > 7.30 without ketosis and is being seen with increasing frequency in adolescent obese children and in some ethnic groups.[6]

Pathophysiology

DKA is seen in 35% to 40% of patients at the time of diagnosing Type 1 diabetes mellitus (DM).[7] Typically, it manifests after the selective destruction of β-cell mass reaches < 10%.[8] The insulin deficiency results in a cascade of metabolic derangements prominent in liver, fat, and muscle. Although infrequent, DKA is now recognized as a complication of Type 2 diabetes.[9]

The counterregulatory hormones secreted in response to insulinopenia—namely, glucagon, epinephrine, cortisol, and growth hormone—initiate de novo enhanced hepatic glycogenolysis and gluconeogenesis to increase blood glucose levels. The latter 2 processes are normally inhibited in the presence of insulin. This coupled with decreased peripheral tissue use of glucose because of the inability of cells to use glucose in the absence of insulin causes high plasma glucose levels. Increased muscle proteolysis also adds amino acids to the hepatic substrate. The ensuing hyperglycemia causes an increase in osmolality resulting in osmotic diuresis.[10] Free water and electrolytes (sodium, potassium, magnesium, and phosphate) are lost in urine along with glucose. This shifts the water

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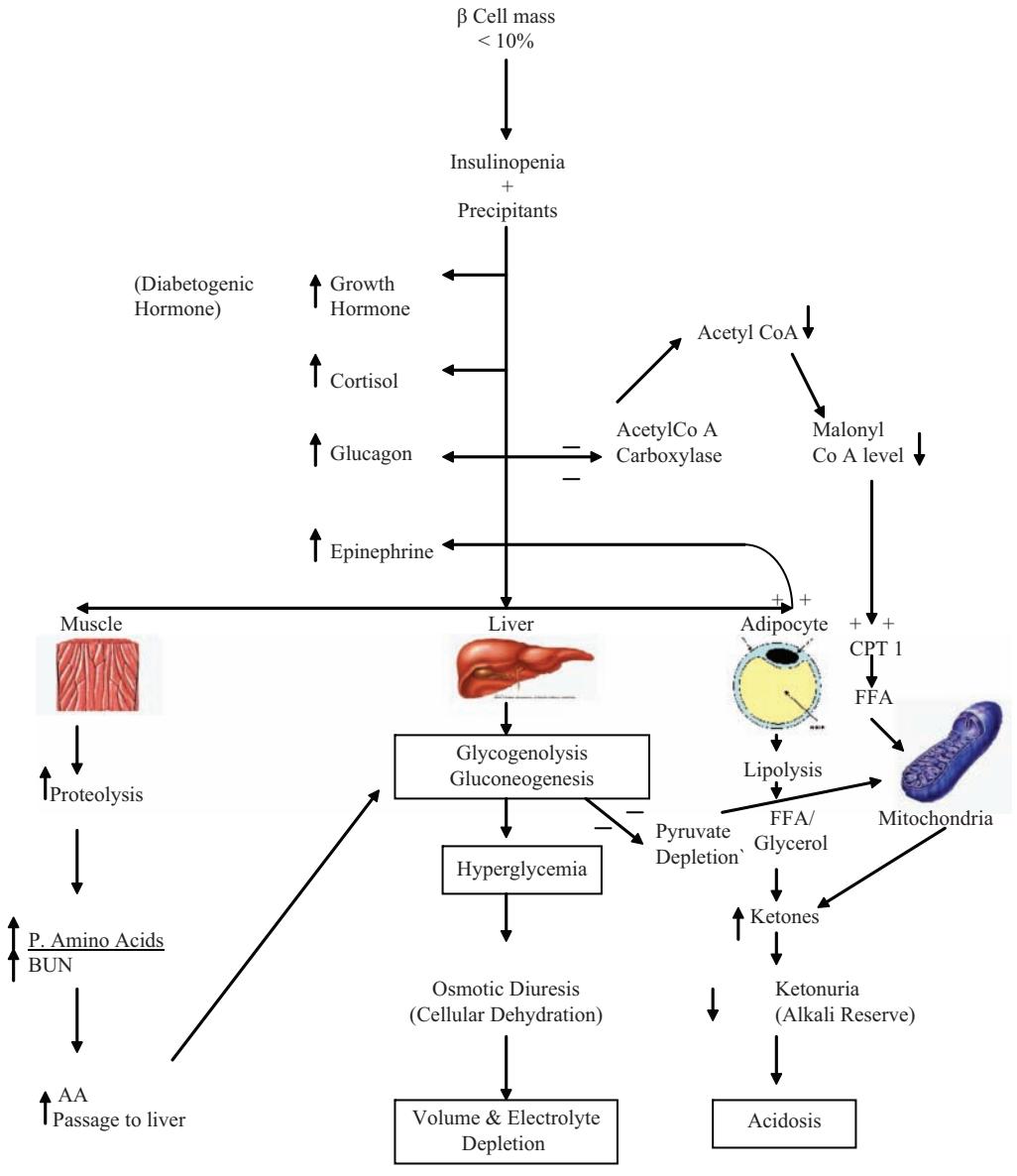

Figure 1. Inhibition and disinhibition.
Note: AA = amino acids; FFA = free fatty acids; - = inhibition; + = disinhibition

from the intracellular fluid compartment to the extracellular fluid compartment, with resultant hyponatremia. Most patients with DKA are hyperkalemic despite the loss of potassium owing to insulinopenia, acidosis, and hyperosmolality.[4]

Hyperketonemia is a product of increased lipolysis. It is secondary to increased activity of lipoprotein lipase whose activity is decreased in the face of low insulin. Catecholamine promotes lipolysis to increase free fatty acids and glycerol in adipocytes. These free fatty acids are the precursors for ketoacid generation in the liver. Glucagon decreases the conversion of acetyl Co A to malonyl Co A by inhibiting the acetyl Co A carboxylase. Low levels of malonyl Co A disinhibit the enzyme CPT I, which causes the free fatty acids to transfer into mitochondria instead of entering the citric acid cycle for oxidation to ketone bodies (Figure 1).

The increase in substrates like fatty acids raises mitochondrial NADH concentrations, leading to a reduction in NADH/NAD ratio, indicating a redox state. This low ratio stimulates the dehydrogenase reactions in β oxidation of fatty acids, with increased formation of ketones, mainly β-hydroxybutyrate.

Pyruvate depletion results as a consequence of its consumption in gluconeogenesis, which prevents free fatty acids from entering the citric acid cycle. Free fatty acids are instead oxidized in mitochondria to form ketone bodies. The ratio in serum of acetoacetate to β-hydroxybutyrate may change significantly from a normal of 3:1, to 7:1 to 15:1. Although ketone bodies are weak acids, because of their significant accumulation, the buffering capacity of the body is overwhelmed and acidosis ensues.

Precipitants

Multiple studies have shown that besides the omission of insulin, including insulin pump malfunction, infections (pneumonia, urinary tract infections, or viral illness) are important precipitating factors.[11] In developing countries, there is a delay in seeking medical attention for varied reasons, and protein energy malnutrition may add to the problems.[12] In a significant percentage of patients, the precipitant may never be identified. Though unsubstantiated, extremes of emotional stress in adolescent age groups are thought to be a psychological precipitant.

Clinical Presentation

The symptoms of DKA are caused by hyperglycemia (polyuria, polydypsia, and nocturia); acidosis (tachypnea or Kussmaul type breathing), and weight loss (loss of body water, which can be up to 6 L). Polyphagia is not a prominent symptom of Type 1 DM. Signs at presentation are those resulting from dehydration, vomiting, and mild epigastric pain[4,7]; the former two can cause hypotension. In some cases, the patient exhibits a fruity breath odor as a result of acetone, and with coffee ground vomitus, hemorrhagic gastritis may be present.[13] Obtunded sensorium is seen with >10% dehydration, particularly in young school-age children. In such children, peripheral vasoconstriction may be responsible for hypothermia.

Socioeconomic Factors

Socioeconomic correlates of preventing the inducement of DKA are especially relevant in developing societies with low educational levels. Educational levels of primary caregivers, for example, mothers or elder siblings of diabetics are very pertinent to the maintenance of glucose homeostasis in diabetics, especially in those who are of school-going age. The use of insulin pumps has added to the complexity of the problem for the caregivers. The constant attention needed from the primary caregiver for proper monitoring of blood glucose, correct administration of insulin, supervision of insulin pump maintenance, or monitoring the diabetic calorie restraints is very critical in the maintenance of glucose homeostasis. Equally important is the timely procurement of diabetic supplies (eg, insulin) and their storage at proper temperatures. Lack of these has been consistently observed in patients with reoccurrences of DKA (personal data). When responsible adults are known to care for their wards, a significant (≈10-fold) reduction in the number of episodes is reported.[14]

Laboratory Parameters

These need to be meticulously monitored to effect interventions in a rapidly changing metabolic milieu. Besides the usual labs, our current practice is to do a blood glucose test hourly till the serum glucose is ≈12 mmol/L, then every 2 hours until it is normal; venous blood gas for pH every 2 hours until it is >7.30; and metabolic panel (Na, K, Cl, HCO_3, Ca, PO_4, BUN [blood urea nitrogen], creatinine, β-hydroxybutyrate) every 4 hours until normal.

The other pertinent etiological evaluations for a new onset of diabetes include determining glutamine decarboxylase (GAD) levels, antiinsulin autoantibody, islet cell antibodies, and antimumps antibody in developing societies. GAD and islet cell antibodies are believed to be responsible for 80% of β–islet cell destruction.[15] About 15% of type 1 patients do not have GAD at the time of diagnosis. Thyroid function tests (free T4 and TSH) should be done because 20% to 30% of children may have associated autoimmune thyroiditis.

With persisting abdominal pain, it is prudent to measure serum amylase and lipase (high sensitivity and specificity at 3 × the value of upper limit of normal) in conjunction with an ultrasound of the abdomen to rule out entities causing acute pancreatitis.[16]

Recently, noninvasive continuous end-tidal CO_2 monitoring was used to monitor any disruption in insulin delivery. The capnogram reveals the steady rise of end-tidal CO_2 to normal; however, with recrudescence in ketoacidosis, the value begins to

decline, indicating a hyperventilating patient. Its value lies in detecting these changes between the scheduled laboratory workup.[17]

The delta (anion) gap may be elevated because of a high level of ketones in circulation. Mixed metabolic disturbances, that is, anion gap metabolic acidosis with metabolic alkalosis, are common in patients with DKA who have persistent vomiting. The vomiting causes loss of hydrogen ions and a potential development of metabolic alkalosis. The ongoing production of ketoacids neutralizes the HCO_3^-, with the resultant bicarbonate level being normal or near normal—hence the need to check for the delta (anion) gap.

Initial sodium levels may be low or high depending on the state of hydration and ADH secretion and may be a warning sign of cerebral edema (CE). The deficit is usually about 5 to 12 mmol/L. Sodium levels do not need to be necessarily corrected for high glucose levels. Initially, a modest degree of hypernatremia may be advantageous to help prevent the fast fall of effective plasma osmolality. Total body potassium deficit is usually 5 to 7 mmol/kg; the replenishment of potassium begins after establishing voiding. However, if potassium is low to begin with, insulin may have to be deferred till a reasonable level is attained. Potassium deficits can be supplemented half each as chloride- and phosphate-containing solutions. If the initial potassium level is <3 meq/L, it should be supplemented in fluids without waiting for urine output.

In addition, calcium, and phosphate levels need to be assessed. Some authors believe that phosphate nonreplacement does not cause any adverse outcomes.[11]Ssevere depletion of phosphate may theoretically cause phosphate depletion syndrome, with resultant decrease in tissue oxygenation resulting from depleted 2,3-diphosphoglycerate; this, however, is rare in clinical practice. Phosphate depletion may persist for several days after resolution of DKA.[3] Creatinine levels may be falsely elevated because ketones interfere with automated creatinine measurements.[11] Serum osmolality measured or calculated may determine the duration of fluid replenishment (vide infra).

HbA1c is an important indicator of glucose control in the preceding 2 to 3 months. With poor glucose control, it is usually >9%; elevation is also observed with recurrent episodes. Urine dipstick checks for the renal spill of ketones, measuring primarily acetoacetate but not the high urinary concentration of β-hydroxybutyrate. The correction of serum β-hydroxybutyrate (N < 300 μmol/L; in DKA ≈ 9100 μmol/L) along with correction of pH and acidosis is one of the end points for termination of IV therapy.

White cell count with a high left shift (15-20 K/mm^3) may be induced by stress hormones or dehydration. Infection is suspected in the appropriate clinical context and/or if white cell count is or exceeds 25 000/μL[18] or if procalcitonin levels are high; however, exclusion by appropriate cultures is imperative. If there is a high index of suspicion for meningitis, the meningitic doses of antibiotics should be given after hemodynamic stabilization; cerebrospinal fluid (CSF) should be evaluated later.

Management

The understanding of fluid and electrolyte homeostasis in DKA was obtained from observations on 2 young adult diabetics.[19] The existing protocols for managing fluid and electrolytes in DKA have evolved from there and were later extrapolated to children. DKA should be, and is often, managed in a critical care unit/high dependency unit, particularly if it is the first episode, if there is severe acidosis, or in those with hemodynamic instability and/or obtunded sensorium (Glasgow coma score [GCS] < 8). A successful outcome depends on meticulous monitoring of rehydration, electrolytes, and insulin therapy and a proactive approach to anticipating CE. Patients may need exhaustive monitoring and nursing care with significant intensivist interventions (Table 1). Children with mild to moderate ketosis and hyperglycemia without vomiting or severe dehydration can be managed in high-dependency areas with properly trained health care providers.[3]

Fluids

The primary goal of rehydration is to establish tissue perfusion for insulin to reach cells. In addition, it also replaces sodium and intracellular fluid water deficits, pushing the glomerular filtration rate to normal, while avoiding CE. This entails meticulous charting of intake and output, which is critical to fluid management. The dehydration deficit estimation is generally believed to be inaccurately calculated to a higher percentage.[20,21] Clinically, it may be easier to use 1.5 to 2 times the maintenance fluid requirements (calculated by the Holliday-Segar method) and adding for the ongoing losses (eg, vomiting). Because patients are

Table 1. Timeline in DKA Management

Time	Examination	Laboratory	Intervention
0-1st Hour	GCS on admission, pupils check, monitor vitals (HR, RR, BP, temperature and pulse oximetry, end-tidal CO2)	CBC, electrolytes (Na, K, Cl, HCO3, BUN, Cr, phosphate), S. -hydroxybutyric acid (HBA). urine ketones, venous pH, blood glucose, and lactic acid level	Calculate total fluid deficit; start careful fluid resuscitation: plasma volume expanders, goal to achieve normal blood pressure; check urine output (may need catheter)
2nd Hour	Check BP and ensure urine output; check GCS every hour for first 8 hours	Check lactic acid in second hour and follow up on labs	Start insulin (with prior check on K levels) and replace fluids (deficit + maintenance evenly distributed over 48 hours.); may need bicarbonate (see text); GCS < 8 or CE: intubate and ventilate; nasogastric tube to suction
	High fever	Suspect infection; check WBC (>15 000/mm3), CRP (high), and urine (WBCs and for nitrates, leukoesterases)	
3-8th Hour	GCS as above; check for ongoing losses	Venous blood for pH every 2 hours; electrolytes (as above), and HBA every 4 hours; may check urine ketones	Send appropriate cultures (blood and urine), use antibiotics with broad coverage
	Continued abdominal pain	Serum amylase and lipase levels; ultrasound abdomen (see text) and abdominal X ray	While continuing insulin, reassess adequacy of fluids and ascertain complete rehydration
9-24th Hour	Check GCS every 2 hours	Can change labs to every 8/12 hours at end of 24 hours	May need to manage acute abdominal pain (pancreatitis)
24-48 Hours	Check GCS every 2 hours if hypernatremia was initially present	Check for pH, electrolytes, and HBA as above and stop if pH, HBA, and HCO3 are normal Continue checking S. Na till low/normal	May need to switch the dextrose concentration, if glucose is 12-14 mmol/L; continue to check for response to ongoing hydration Complete rehydration at 48-hour period; transition to pump or subcutaneous insulin

ECF contracted, most often dehydration is ≈10% to 15 % (with hypotension); hence, physiological saline boluses can be used in increments of 10 mL/kg till the blood pressure (BP) normalizes. The normalization of hypotension (cap refill < 3 s) is imperative within the initial hour of presentation while avoiding the use of hypotonic fluids. Replacement fluids may decrease the blood glucose by up to 23% because of increased renal perfusion and loss of glucose in urine.[22] Initially, the pH may decrease slightly because of dilution of the lactic acid in the intravascular compartment. Normal saline may overcorrect the hyperchloremic state, which can persist for several days; however, with normal renal function, it self-corrects. Fluid deficits should be replaced at an even rate over 48 hours. The type of fluid administration after the first hour of normal saline is based on the sliding scale of glucose levels and the corrected sodium calculated. If the serum sodium is low, normal saline is used; however, if it is normal or high, then 0.45% normal saline is given. For ease of administration, the double-bag system may be used; this includes the change that is made to dextrose 5% in 0.45% normal saline when glucose levels are 12 to 14 mmol/L (see below).

That total fluid administered should not exceed 4 L/m^2/24 h for fear of causing CE is most often the mainstay of therapy in many pediatric critical care unit protocols.[23,24] This may not be the case when the patient is transferred from outlying emergency rooms, where patients tend to receive more of hypotonic fluids. However, the recent data of Felner and White[25] showed that an increase in the amount of fluid administered (5.3 L/m^2/24 h) did not change the incidence of CE. In their study, the incidence of CE was lower (0.3%) than that reported in other studies (3%).[26] Most often rehydration is usually achieved in

36 hours, except in hypernatremia, where it is done over a 48-hour period. Harris and Fiordalsi[27] in their data on childhood DKA observed no death or near-death episodes in patients rehydrated over 48 hours. One rule of thumb is to deliver fluids (deficit and maintenance) over a period of 48 hours if serum osmolality > 360 mosm/L. Because high initial osmolality may be a harbinger of death in these children, slow infusions may be prudent to avoid large falls in effective plasma osmolality.[7,11,28] The progress of DKA is followed by monitoring acidosis (HCO_3 > 18 meq/L), rise in pH (>7.30), and decreasing ketones in blood. Complete biochemical recovery, more often than not is attained in 48 hours, when insulin is changed to a subcutaneous route.

Insulin

Regular insulin (0.1 unit/kg/h) infusion is started and continued till pH and the bicarbonate level are corrected (>7.30 and >15, respectively), serum ketonemia (β-hydroxylbutyrate) is normal, and the glucose level is 8.4 to 12 mmol/L. This dose of insulin is given to attain a steady-state plasma level of 100 to 200 μmol/mL in 60 minutes and is enough to stop lipogenesis and ketogenesis and increase peripheral glucose uptake.[29] Young children may be started with a lower dose of insulin (0.05 unit/kg).

Very rarely an insulin bolus may be used in situations where the initiation of treatment is significantly delayed. On a sliding scale basis, after the start of the insulin infusion, dextrose in the saline needs to be adjusted for the drop in blood glucose. A drop of ≈5.5 mmol/h in glucose levels is believed to be sufficient to inhibit the metabolic pathophysiology of DKA[7]; hence a drop of >6 mmol/L should clearly be avoided. After these glucose levels are achieved, it usually takes 5 to 7 hours for ketosis to clear.

In patients younger than 4 years of age there is a prolonged time lag for plasma glucose levels to reach 12 to 14 mmol/L, presumably because young children and adolescents, who have high growth velocity, have higher levels of the human growth hormone, a diabetogenic hormone. Also, patients with fever or infections and higher metabolic requirements may need 15% to 20% more insulin than the usual starting dose.

Acidosis

Lactic acidosis may result from tissue hypoxia and, because of the renal compensation, may be overwhelmed by excess production of H^+ ions. Although there is no consensus regarding the use of bicarbonate, with a pH of <6.9 correction may be needed, especially if after appropriate fluid correction and combating hypotension and/or shock, the pH persists at <7.00 or low levels of bicarbonate remain (< 5mmol/L for >10 hours) after the start of hydration. The reason to combat acidosis is to reduce or negate the insulin resistance, negative inotropism, and peripheral vasodilatation. Before undertaking the change of insulin infusion (usually in a ratio of 1:1 with normal saline), insulin dilution and rate of insulin administration needs to be rechecked. Fast bicarbonate IV administration should be avoided, as it can potentially cause alkalotic tetany or seizures, besides adding to hyperosmolality, hypernatremia, and hypokalemia with aberrant ventricular rhythms. Bicarbonate may be infused (0.5-1 meq/kg) over a period of 1 hour and then rechecked again.[30]

Complications

1. CE, the hypotheses extended for it's pathogenesis are the following:

    a. Na/H antiport transporter on cell membranes are activated, with exchange of excess H^+ ions for extracellular sodium: the increased intracellular sodium increases the cell volume during rehydration.
    b. Excess ketoacids, resulting from prolonged antecedent ketosis, and/or persistent severe acidosis are present.[7]
    c. Persistent glucose-induced hypertonicity is implicated in causing neural cells to produce osmotically active idiogenic molecules (myoinstol and taurine). Whether their production follows or precedes the therapy is debated. This reflects a possible neural protective mechanism, adapted in the face of significant hyperosmolar conditions, and once formed these molecules dissipate slowly over 12 to 24 hours.[31,32] While serum osmolarity is rapidly decreasing, the relative hyperosmolarity in the neurons shifts the fluid into them, probably more so in the presence of insulin. Hypertonicity, in addition, may compromise cerebral vascular endothelial tight junctions. Rapid reduction in plasma osmolality, by administering free water, creates a gradient causing water to move into neural cells, which then causes them to swell up.

d. Glaser et al[33] performed a brain perfusion scan and MRI in patients with DKA. They documented high elevations of an apparent diffusion coefficient (which indicates water diffusion), strongly suggesting a vasogenic origin of edema. This view was endorsed by Tasker et al[34] while explaining the pathophysiological basis of hyperventilation in DKA patients with CE and is also consistent with the increase in proinflammatory cytokines, which decrease when insulin is on board.[35] Whether the CE is present in all patients, if it is the hyperosmolality per se (cytotoxic edema) or the disruption it creates in the endothelial CSF barrier, if it is vasogenic edema by a different mechanism, or if it is a combination thereof is unclear and debated. This truth is brought into focus by the pattern of focal injury that is found in high adenosinetriphosphate demand areas of the brain, that is, mesial basal ganglia and thalamus, periaqueductal gray matter, and dorsal pontine nuclei seen as a basilar swelling on CT scan of the brain.

Risk factors for CE include age < 5 years, high initial BUN reflecting severe prolonged state of dehydration, hyperventilation to a $PaCO_2$ of ≤22 mm Hg[34] and presenting arterial pH of < 7.00.[36] Of these, high initial BUN and a very low initial $PaCO_2$ are considered clinically and statistically more relevant, whereas epidemiologically, younger age and new onset type 1 DM are important.[3]

CE presents 4 to 8 hours after the start of rehydration therapy and may present as late as 22 to 30 hours after the start. Presentation may be abrupt with sudden severe headache, vomiting, sudden hypertension, and obtunded sensorium. Anisocoria, ophthalmoplegia, posturing, and seizures may also be observed.[9,34] Very frequently, mild CE may be seen on brain imaging while the patient is on the way to recovery.[8] Hence, very frequent neurological monitoring (every 1 hour) may be needed, which may include the GCS and pupil size and reaction. However, in a retrospective study, the excessive reliance on the GCS to monitor for CE in DKA was commented on.[31] Early signs of neurocompromise are apt to be missed with the use of the GCS, for example, age-inappropriate incontinence, sustained heart rate deceleration >20 bpm, headache and vomiting, and diastolic BP > 90 mm Hg. The authors put forth a bedside criterion of evaluating the neurological state of such children, which however remains to be validated prospectively.[37]

Serum S-100 β-protein has been identified as a potential marker for CE, whose rise is pari passu with the worsening of CE (normal-0.12 μg/L).[40]

The first management response to CE is to elevate the head of the patient to 30°, followed by IV mannitol (1 gm/kg and repeated 15 minutes later). Currently, there are few reports of the use of hypertonic saline solution for CE (3% sodium chloride: 10 mL/kg over 30 minutes and repeated in 2 hours).[38] This should be followed by rapid sequence intubation (lidocaine-midazolam- rocuronium) and hyperventilation to maintain $PaCO_2 \approx 30$ mm Hg and, finally, cutting back of the maintenance fluids to 75% of the amount required.

Based on the previous cumulative literature of CE in DKA, Tasker et al,[34] presented an interesting hypothesis in a hypocapnic-acidotic DKA patient with CE. The CSF pH determines the cerebral blood flow. In DKA, low CSF HCO_3 and compensatory hyperventilation lowers $PaCO_2$ and maintains relatively high CSF pH. Therefore, in DKA, if the normalization of $PaCO_2$ is achieved quickly by the use of ventilation to achieve low $PaCO_2$, then the CSF $PaCO_2$ will increase, the CSF pH will stay low, and the brain will become hyperemic. The authors recommend not interfering with the CSF adaptive physiology to try to lower the bicarbonate. They further advocate that intubation and ventilation in CE with DKA should only be done for exhaustion, with a target level of $PaCO_2$ appropriate for estimated CSF bicarbonate (HCO_3 CSF), based on their mathematical model: $[HCO_3]CSF = 0.9 \times [HCO_3]arterial + 4$; CSF $PaCO_2 = 0.95 \times PaCO_2 = 6.7$. Simply put, symptomatic CE patients should be ventilated to a $PaCO_2$ level present at the time of intubation. Other studies seem to support this hypothesis.[39] Only after these measures are undertaken should one get a CT of the brain. Hyperventilation in any case is a temporizing measure and, if prolonged, can potentially be harmful.

In an early timeline with suspected CE, the use of mannitol may be inappropriate when resuscitation is still ongoing; hypertonic (3%) saline can be considered as an alternative. Concerns regarding the use of 3% saline, that is, hypernatremia, hyperosmolality, and central pontine myelinosis remain. Besides the effects of high sodium in increasing the risk of renal failure, pulmonary edema, congestive heart failure, and neurological complications are potential problems. However, 3% saline has been used in the setting of brain trauma more often, and these adverse biochemical events are believed to be

more of academic concern rather than potential prospective clinical problems.

2. Alkalotic tetany (resulting from fast correction of severe acidemia) occurs with the use of sodium bicarbonate. It can present as a tingling sensation of the perioral area including the tongue. In extreme cases, this can cause carpopedal spasm. Ionic calcium needs to be checked and corrected if low.
3. An important though rare complication includes rhabdomyolysis as a result of muscle proteolysis. If suspected on the basis of cola-colored urine without any red cells, check creatinine phosphokinase. Most often hydration and alkalinization of urine and/or use of mannitol without recourse to continuous venovenous filtration can help excrete myoglobin safely.
4. Acute respiratory distress syndrome: noncardiogenic pulmonary edema may occur from excessive fluid administration.[12]
5. Thromboembolism: the hypercoagulable state in DKA is enhanced by subclinical endothelial injury, hypofibrinolysis, and platelet aggregation. The elevated levels of procoagulant factors (plasminogen activator inhibitor-1) and other proinflammatory cytokines lends credence to this view, while explaining the link between hyperglycemia and thromboembolism. Insulin may restore these high levels of cytokines to normal.[41-44]
6. Hypoglycemia and hypokalemia may especially be seen in severely malnourished children in developing countries.[12] Whereas hyperkalemia is a result of the reduced glomerular filtration rate early in the course of DKA, hypokalemia may be because of a prolonged course of illness.
7. Rarely, mucor infection is seen: in the setting of recurrent DKA, especially infections of sinuses and upper airways, it is often fatal.[45]
8. Arthralgias lasting >24 hours following completion of insulin therapy are usually transitory (personal data).

Insulin Transition

The transition to subcutaneous insulin is achieved with the patient being alert and retaining clear fluids, with hyperglycemia and acidosis resolved (pH > 7.3, bicarbonate > 15 meq/L), and with β-hydroxy butyrate levels becoming normal. Once this is established, it is time to discontinue IV insulin and glucose. Prebreakfast glucose value is sought; regular insulin (known diabetic patients revert to their old insulin regimen) is given 15 to 30 minutes before breakfast (part of diabetic diet), and then, ADA oral diet is offered; 30 to 60 minutes later, the insulin infusion is stopped. This sequencing is essential, for it allows smooth transitioning to subcutaneous insulin and also prevents the patient from sliding back into ketoacidosis.

DKA in Type 2 Diabetes Mellitus

Recently, an attempt has been made to enunciate clinical and biochemical differences in DKA with type 1 and type 2 DM.[46] The study included 138 adult DKA patients, of whom 30 had type 2 DM. DKA in type 1 DM patients was mostly a result of discontinuation of the insulin; whereas infections were the reason in type 2 DM patients. Although acidosis was more common in type 1 DM, type 2 DM required prolonged insulin infusion to produce ketone-free urine, implying insulin resistance or relative insulin deficiency. However, the overall management in both these types was quite similar to that elucidated here.

Safety

The management of DKA is prone to medical errors. It is prudent for 2 observers to do fluid calculations separately. The infusion solutions needed (5% or 10% dextrose with electrolytes) should preferably be available as premixed solutions to avoid potential errors. Meticulous charting and labeling of insulin infusion is imperative, including charting for fluid input and output. A clear management protocol in the unit may be necessary to avoid problems.

Formulae

Total body water deficit
= 0.6 × Weight × (1 − 140/serum.Na)
Corrected plasma (P) sodium
= P Na + (1.6/5.5) × (P Glucose − 5.5)
Calculated plasma osmolality
= 2 Na + P Glucose (mmol/L) + P Urea (mmol/L)
Anion gap (not applicable if flame photometry is used to measure electrolytes)
= Na − Cl + HCO_3 (normal = 6.6 to 10.6)
= adjust for albumin: add 2.5 for each1 gm of albumin below level of 4 gm/dL)
Delta anion gap = anion gap − 7

Fluids and Sliding Scale

We used a double-bag system for IV fluids; 1st bag 0.9% normal saline (NS), with 20 meq K Phos/L and 20 meq KCl/L; 2nd bag with dextrose (D) 10% ½ NS, with 20 meq K Phos and 20 meq KCl/L. We used it as follows: glucose > 13.8 mmol/L (250 mg/dL), infuse 0.9% NS at the hourly rate of fluids calculated; glucose < 13.8 mmol/L (250 mg/dL), infuse 50% of hourly rate of fluids calculated from each bag; glucose < 8.33 mmol/L (150 mg/dL), use D 10% alone at the hourly rate of fluids calculated.

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