

The Role of Renal Regulatory Mechanisms in the Evolution and Treatment of Pediatric Diabetic Ketoacidosis

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ABSTRACT

Diabetic ketoacidosis (DKA) is a life threatening complication of diabetes mellitus in pediatric patients with new onset insulin dependent diabetes. Despite advances in therapy mortality from DKA, especially in children less than two years, remains high. This review highlights the role of obligatory renal defense mechanisms in the evolution of DKA and its implication for therapy: to accomplish this goal the review starts with a cursory description of the pathogenesis and pathophysiology of metabolic derangements in DKA as a basis for understanding the renal compensatory mechanisms geared towards restoration of acid-base balance; then, the next section of the review describes how alterations in fluid and electrolyte balance at the onset of DKA and the extent of renal regulatory defense mechanisms geared towards its restoration can predispose to cerebral edema at the beginning of therapy. We conclude by suggesting that restoration of fluid and electrolyte balance should be based on the severity of metabolic acidosis as determined by the extent of renal impairment at the onset and during the course of DKA rather than strictly by protocols.

Keywords: Diabetic Ketoacidosis; Pediatrics; Hyperosmolar; Cerebral Edema; Hyperglycemia; Hyperkalemia

1. Introduction

About half a million children worldwide are estimated to have diabetes mellitus [1] and the incidence of insulin dependent diabetes mellitus (IDDM) is increasing by about 3% (range 2% - 5%) per year with a higher incidence in children less than four years [1]. Data from a United States study showed that youngest children (less than 2 years) were at greatest risk, with over 37.3% presenting with diabetic ketoacidosis (DKA) compared to 14.7% in those aged 15 - 19 years [2]. A multicenter European study showed widely varying incident rate of 26% - 67% in patients with IDDM [3]. Worldwide, newly diagnosed cases of IDDM with DKA occur predominantly among children in the most deprived communities especially ethnic minorities with poor access to health care [3,4]. Despite advances in management over the past 20 years the incidence of mortality associated with DKA remains unacceptably high compared to the general population particularly in the age group 1 - 4 years [5]. Recent reported mortality rate in national

population-based studies is 0.31% in United Kingdom [5] and 0.15% in United States [6]. In developing countries mortality rates are higher due to higher rates of infection, protein-energy malnutrition and delay in seeking medical care [7]. The objectives of this review are: 1) to acquaint the reader with the pathogenesis and pathophysiology of IDDM as a basis for understanding the fluid and electrolyte derangements in DKA; 2) to discuss the role of renal regulatory mechanisms in the evolution DKA and the predisposition to cerebral edema at the onset of therapy.

Pathogenesis of IDDM. The etiology of IDDM is thought to be autoimmune, possibly through interplay of genetic predisposition and environmental factors like viral infections. Autoimmune destruction of insulin producing beta cells of the pancreas can be initiated by infection of any cell in the body by a virus whose proteins share an amino acid sequence with a beta cell protein or by direct viral infection of a beta cell with subsequent release of cytokines (e.g. interferon- α) and the adhesion of leukocytes within the pancreatic islets [8]. In a recent study 17.8% of children (less than 21 years of age) with DKA have presumed viral infection and 12.9% had bac-

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terial infection [9]. Once the autoimmune process is triggered by infection, destruction of beta cells occurs via various effector mechanisms like antibody dependent cellular cytotoxicity, delayed hypersensitivity and complement activation. Factors regulating the speed of autoimmune destruction of beta-cells include genetic predisposition (HLA subtype), increased metabolic activity of beta cells (pubertal growth spurt) and the age at which the child encountered the precipitating event. Histological studies suggest that 80% reduction in volume of beta cells is required to develop symptomatic IDDM from pancreatic beta cell failure [10].

Pathophysiology. The two events that can precipitate DKA are either absolute lack of insulin due to pancreatic beta cell failure or relative insulin deficiency from excess counter regulatory hormone secretion in response to stress [11,12]. In the absence of insulin, a catabolic state ensues in the liver, adipose tissues and skeletal muscle cells. Insulin regulates production of ketones through its action on hepatic, adipose and peripheral tissues. Insulin inhibits lipolysis in adipose tissues, while it enables esterification of free fatty acids in the liver and stimulates oxidation of ketones in muscle cell [11,12]. Insulin deficiency initiates metabolic derangements resulting in hyperketonemia due to both overproduction and decreased utilization of ketones. Ketogenesis is further stimulated by glucagon through oxidation of fatty acids in the liver. Severe dehydration due to osmotic diuresis and other metabolic changes in DKA leads to release of counter-regulatory hormones like catecholamines, renin, aldosterone, arginine vasopressin in order to restore intravascular volume [12]. The resulting hormonal imbalance leads to insulin resistance and stimulation of gluconeogenesis, ketogenesis, and lipolysis [12].

Hyperglycemia. Results from impaired glucose utilization by most tissues and increased hepatic glucose production due to insulin deficiency and increased level of glucagon. An elevated glucagon/insulin ratio causes a drop in fructose 2,6-biphosphate concentration, resulting in inactivation of phosphofructokinase and activation of fructose 1-6-biphosphatase; the end result is enhanced gluconeogenesis and clinical hyperglycemia [12]. Hyperglycemia leads to osmotic diuresis and glycosuria in patients with DKA.

2. Fluid and Electrolyte Losses

Extracellular Fluid Compartment. Hyperglycemia causes increased effective osmotic pressure of the extracellular fluid (ECF) compartment leading to osmotic shift of water out of skeletal muscle cells [13]. The increased filtered load of glucose from hyperglycemia exceeds renal tubular reabsorptive capacity leading to significant glycosuria and osmotic diuresis [13]. However ECF volume expansion from hyperglycemia is transient because

vomiting and osmotic diuresis ultimately leads to volume depletion. Progressive rise in serum osmolality occurs in DKA because urinary water losses and extra renal fluid losses exceed electrolyte losses [13]. Pre-renal azotemia due to volume depletion is a classic finding in DKA and levels of blood urea nitrogen (BUN), creatinine, total proteins, uric acid, hematocrit and hemoglobin are elevated in severe DKA due to ECF volume contraction [13]. The typical water and electrolyte deficits in DKA and their therapeutic implications are outlined in (Table 1).

Sodium & Chloride Losses. Serum sodium may be normal, high or low on presentation in patients with DKA. High serum sodium and chloride may result from ECF volume contraction because osmotic diuresis due to hyperglycemia counterbalances dilution of these electrolytes that could result from movement of water into the ECF from the intracellular fluid (ICF) compartment [13]. Urinary losses of sodium from osmotic diuresis exceed chloride losses because most of the urinary anions are ketones rather than chloride but vomiting may magnify chloride losses (13). Low serum sodium usually results from the following mechanisms: 1) water movement into the ECF from ICF because of hyperglycemia; movement of sodium from ECF to ICF in replacement of potassium losses; 2) reduced ability to excrete ingested water because vasopressin is released in response to ECF volume contraction [13,14]. Absence of hyponatremia in a child with severe DKA in the presence of significant hyperglycemia implies low intake of water due to a decreased ability to obtain or ingest water as a result of impaired sensorium or coma [14]. Persistent hyponatremia in DKA after correcting for hyperglycemia is usually the result of excessive administration of fluid [15]. Also, serum sodium is spuriously low in presence of hyperlipidemia because the aqueous phase of blood in which sodium predominantly resides is decreased in extreme lipemia [16,17]. True plasma sodium can be calculated from the formula: True (Na) (0.021[T] + 0.994) where T equals the triglyceride level in g/dL and sodium is expressed in mEq/L [17,18].

Potassium Losses. Serum potassium levels in DKA may range from normal to high and occasionally attaining lethal levels. Varying degrees of total body potassium depletion occurs mainly from massive kaliuresis, decreased intake and frequent vomiting [19-21]. Because potassium is the principal cation in the ICF compartment, it is retained intracellularly by an electrical negative voltage created by $\text{Na}^+\text{-K}^+$, ATPase [20,21]. This voltage is diminished in an insulin-deficient state therefore K^+ is redistributed from ICF to ECF compartment in DKA. Increased effective serum osmolality characteristic of DKA contributes to hyperkalemia due to translocation of potassium rich fluid from the ICF to ECF compartment [20,21]. However, critical hypokalemia following insulin

Table 1. Typical deficits in a patient with diabetic ketoacidosis.

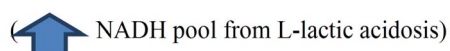
	Quantity	Comment	Clinical implications
^a Na ⁺	3 - 9 mmol/kg	Restore Na ⁺ deficit slowly	Low initial serum sodium and its failure to rise with therapy or a rapid correction of sodium deficit have been linked to risk of cerebral edema
^a K ⁺	4 - 6 mmol/kg	Follow plasma potassium concentration closely; must await insulin action to shift potassium into cells and improved renal function before potassium supplementation	Fatal hypokalemia may occur with insulin therapy in presence of hyperglycemia
Water	4 - 6 liters	Half ^c ICF, half ^d ECF	Rapid correction of water deficit or sudden changes in plasma osmolality are risk factors for cerebral edema
Bicarbonate	Can be >500 mmol of H ⁺ buffered	If increased anion gap, need not give bicarbonate unless very severe acidosis	Bicarbonate administration has been linked to onset of cerebral edema; routine use in DKA therapy is discouraged

^aNa⁺, sodium; ^bK⁺, potassium; ^cICF, intracellular fluid; ^dECF, extracellular fluid. Adapted with permission from authors, Dubose & Hamm [62].

administration can occur in DKA because of existing total body deficit of K⁺ from vomiting and increased renal losses [22].

Phosphate Losses. Serum phosphate levels fluctuate widely in patients with DKA despite overall depletion in body phosphate stores [23]. Initially, the apparently high or normal phosphate levels on admission correlate positively with the serum effective osmolality, serum glucose concentration and degree of acidosis because academia induces release of phosphate from cells. However, a drop in phosphate level usually occurs with insulin and fluid therapy; renal mechanisms of hypophosphatemia in DKA include: 1) inhibition of phosphate reabsorption from the proximal tubule by high glucose concentration in the filtrate; 2) decrease filtrate concentration of sodium, low urinary pH and osmotic diuresis [23,24]. Hypocalcemia and hypomagnesemia are potential complications resulting from routine administration of phosphate in DKA patients with hypophosphatemia [24].

Acid-Base Changes. Increased fatty acid pool in DKA [25] leads to over production of acetoacetate (H.AcAc) and B-hydroxybutyric acid (H.B-HB) in the liver. Hydrogen ions (H⁺) are consumed by conversion of H.AcAc to acetone which is eliminated via the lungs and is in part responsible for removal of ketoacids [26]. A high redox potential (nicotinamide adenine dinucleotide; NADH-to-NAD⁺) from hypoperfusion and lactic acidosis during DKA leads to the body's inability to eliminate ketoacids by the acetone route; as a result, a shift in the equilibrium between H.AcAc and H.B-HB towards H.B-HB production occurs as shown in the equation below.



The resultant accumulation of H.β-HB in excess of

H.AcAc (3:1 molar ratio) leads to increased plasma unmeasured anions [27] or anion gap (AG). The AG (normal, 12 ± 2 mEq/L.) refers to plasma anions other than chloride and bicarbonate that balance the positive charges of sodium and potassium. Ketoacids anions are buffered by bicarbonate resulting in an increased AG metabolic acidosis [28,29]. Also, a mixture of AG metabolic acidosis and hyperchloremic acidosis (HCA) can occur in DKA because of significant urinary losses of ketone salts of sodium and potassium with retention of chloride [30, **Figure 1**]. HCA can also result from: 1) excessive use of chloride rich isotonic fluids; 2) correction of potassium deficits with potassium chloride; in the latter case, uptake of potassium in exchange for ICF hydrogen ions (H⁺) result in net increase in ECF chloride because of bicarbonate buffering of the H⁺ [30].

Issues for Management. DKA can be diagnosed purely on clinical grounds (weight loss, polyuria, polydipsia, lethargy or coma) and with the aid of the laboratory tests shown in (**Table 2**). In order to avoid treatment related errors in DKA the following issues must be considered: 1) accuracy of the clinical estimates of dehydration; 2) rate of fluid repletion; 3) the extent of renal impairment and its implication for fluid and insulin therapy in DKA; 4) risk of cerebral edema resulting from fluid repletion and insulin therapy especially in the setting of renal impairment.

Estimation and Replacement of Fluid Losses. Clinical assessment of fluid deficits and its rate of repletion are diverse in DKA depending on the specialty training and bias of the treating physician [31]. Evidence from recent studies revealed an overestimation of fluid deficits in most patients with DKA [32,33]. In a study by Fagan *et al.* [32] data from 33 episodes of DKA showed that majority of patients had moderate (4% - 8%) dehydration using percent loss of body weight but by clinical assessment the degree of dehydration was overestimated in

67% of patients in the study. In a study by Koves *et al.* [33], there was a significant difference between assessed and measured dehydration: while the median absolute measure of dehydration calculated by patients' weight gain in their study was 8.7% fluid deficit was overestimated in 24% of their patients [33]. The authors concluded that clinical assessment of dehydration in DKA is complicated by the extent of water deficit in ICF and ECF compartments, the overall catabolic state of the patient and the effects of metabolic acidosis on the clinical signs of dehydration. Moreover, weight loss (a valid measure of dehydration) could result from increased catabolism due to insulin deficiency and not solely from severe dehydration [32-34]. Apart from inaccurate assessment of the degree of dehydration, published reports indicate that physicians do not always follow established guidelines on fluid repletion and are apt to giving large volumes of fluid during treatment for DKA [35,36].

Renal Impairment in DKA. Hypovolemia causes varying degrees of renal impairment in DKA due to reduction in renal blood flow (RBF) and glomerular filtration rate (GFR) [37,38]; BUN and plasma creatinine varies inversely with GFR, increasing as the GFR falls in severe hypovolemia [39]. Volume depletion leads to passive reabsorption of urea along with sodium in the proximal tubules. The net effect is a fall in urea excretion and elevation in BUN and BUN/plasma creatinine ration [39]. Concomitant reduction in plasma volume from dehydration is associated with elevation in hematocrit and plasma albumin concentrations since both red cells and albumin are limited to the vascular space [39]. The effective osmolality of the plasma (P_{osm}) is determined to a large extent by renal regulation of solutes (sodium, po-

tassium, glucose, and urea) and water [39]. Insulin therapy and the extent of renal impairment can determine the extent of changes in P_{osm} with dire consequences in DKA. For ease of management, DKA patients can be categorized into two groups (**Figure 2**) based on renal indices and the pattern of acid-base disturbances on admission [40]: 1) those with significant renal impairment, as shown by higher elevations of BUN, creatinine, albumin and hematocrit; 2) those with mild renal impairment, as shown by slight elevations in BUN, creatinine, albumin and hematocrit [40]. Typical patterns of acidbase disorders in DKA include AG metabolic acidosis and or HCA. While HCA is due to urinary excretion of ketone salts (loss of bicarbonate precursors) and retention of chloride in patients with relatively preserved renal function, AG acidosis, on the other hand, occurs in those with severe DKA and renal insufficiency [40]. In order to determine severity of metabolic acidosis as a guide to subsequent therapy, a distinction between the two subsets of DKA patients can be made by initial assessment of the ratio of excess AG to bicarbonate (Δ/Δ ratio): where excess AG (mEq/L) equals measured AG minus normal AG (ΔAG); and bicarbonate deficit (mEq/L) equals normal plasma bicarbonate minus measured plasma bicarbonate (ΔHcO_3). Expected Δ/Δ ratio is 1.0 since the bicarbonate deficit is the result of its titration by ketoacids ([40], **Table 3**). Values above unity indicate severe ECF volume deficit and renal impairment as seen in DKA patients with pure AG acidosis compared to those with HCA [40]. The adequacy of renal function is an important determinant of rise in AG from ketoacidosis. In DKA patients without renal impairment, there is a minimal rise in anion gap and the Δ/Δ ratio is <1 because filtered ketoacids

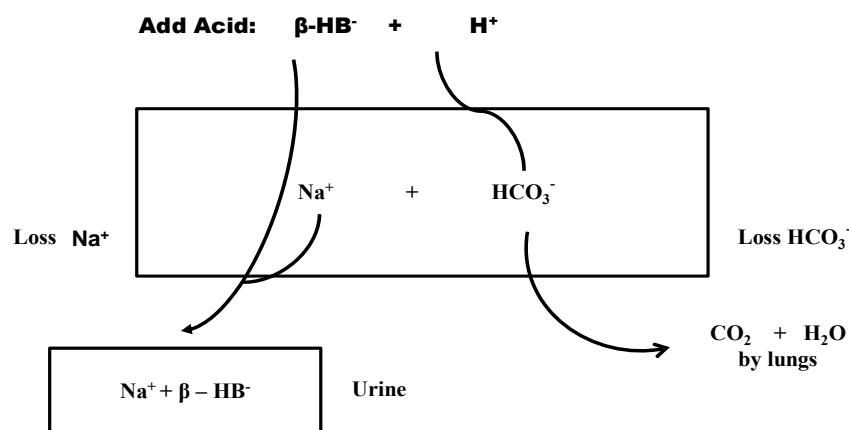


Figure 1. Development of hyperchloremic metabolic acidosis (non anion gap) in DKA from indirect loss of bicarbonate precursors as sodium salts of ketoacids. The rectangle depicts the body, and it contains Na^+ and HCO_3^- ions. When β -hydroxybutyric acid ($\text{H.A.}\beta\text{HB}$) is added, its H^+ is removed by reacting with HCO_3^- . The anion (βHB^-) is excreted along with Na^+ for electroneutrality. This excretion occurs when the urine contains more βHB^- than NH_4^+ . Patients with relatively normal GFR excretes ketoacids load (βHB^- anion) that exceeds renal tubular reabsorptive capacity thereby *minimizing* rise in anion gap (AG). AG is higher when renal function is impaired because of retention of βHB^- . GFR ; glomerular filtration rate. Reproduced with permission from Dubose & Hamm [62].

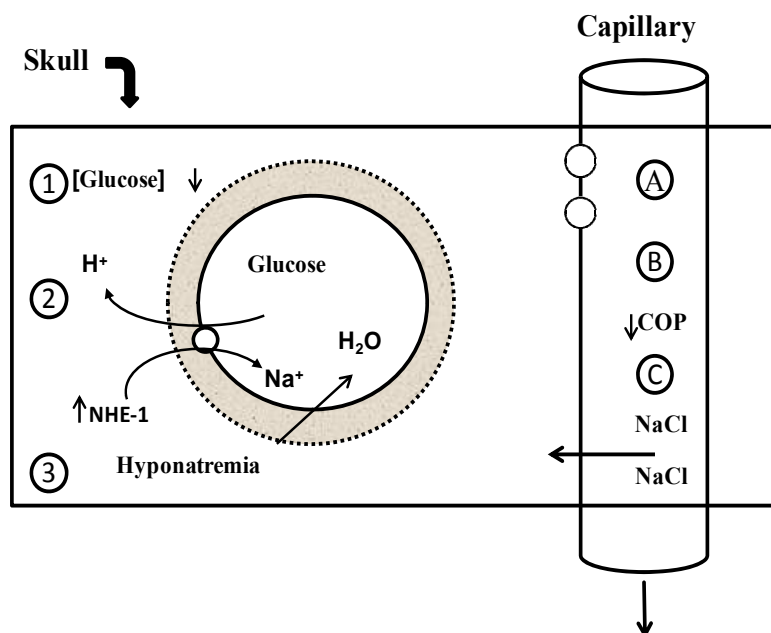


Figure 2. Risk factors for cerebral edema: the solid rectangle represents the skull. The three risk factors for swelling of brain cells are shown on the left and include a higher concentration of glucose or its metabolites in the brain due to rapid lowering of the blood glucose level (site 1), activation of the Na⁺:H⁺ exchanger-1 (NHE-1) by insulin (site 2), and the development of hyponatremia (site 3). The factors causing expansion of the extracellular fluid volume of the brain are shown on the right and could be the result of less restrictive blood brain barrier (site A), a fall in the colloid osmotic pressure (COP) in plasma (site B), or excessive administration of saline (site C). Reproduced with permission from Dubose and Hamm [62].

exceeds tubular reabsorptive capacity with resultant excretion of large quantities of ketoacids anions [40]. This is in sharp contrast to DKA patients with low GFR from renal impairment in whom retention of β -hydroxybutyric acid leads to increased AG and a rise in Δ/Δ ratio above unity because elevation in aniongap exceeds fall in plasma bicarbonate concentration ([40], **Table 3**). Therefore, DKA patients with pure AG acidosis are prone to more complications compared to patient with HCA [40]. The longer the duration of acid-base stress and the extent of renal and other regulatory defense mechanisms geared towards its restoration, the higher the risks of cardio-respiratory and central nervous system (CNS) complications in DKA. Complications arise as a result of dehydration, hyperosmolality and metabolic acidosis: for example, compensatory hyperventilation in severe metabolic acidosis is associated with increased respiratory work load and risk of respiratory failure in DKA [41]. Also, a higher risk of cerebral edema and hypoxic-ischemic CNS injury in DKA has been linked to the severity of hypocarbia on admission due to reduction in cerebral blood flow from vasoconstriction [42].

Implications for Therapy. Majority of protocols for management of DKA in children are based on the assumption of a normal renal function [43]. Recent consensus guidelines allude to renal impairment in DKA without recommending changes in fluid management to

reflect decreased renal function [44,45]. Clinicians must be cognizant of the association between occurrence of cerebral edema in DKA (CE-DKA) and factors like rate of fluid administration and changes in effective osmolality of plasma (P_{osm}) during DKA therapy [45]. CE-DKA occurs in 0.5% - 1% of DKA patients especially in those less than 5 yrs old and it is associated with a high mortality rate of 20% - 90% [46,47]. Though studies [48, 49] have shown evidence of subclinical CE-DKA even before commencement of therapy, results of animal and human studies [50,51] demonstrate increased intracranial pressure (ICP) as fluids are administered in DKA. Other authors have postulated existence of a possible association between occurrence of symptomatic CE-DKA and a drop in effective P_{osm} within 4 - 12 hrs of fluid therapy [52,53]. To underscore the association of CE-DKA with institution of fluid therapy, factors determining changes in P_{osm} prior to admission and at beginning of therapy must be considered based on the relationship between plasma sodium concentration and total body water. This relationship is expressed in the following equation as: $Plasma (Na^+) = Nae^+ + Ke^+/TBW$; Nae^+ and Ke^+ refers to the osmotically active quantities of sodium and potassium; TBW refers to total body water [54]. In patients with DKA, factors likely to increase P_{osm} begin prior to admission and at initiation of therapy as outlined in (**Table 4**). Pre-admission factors lead to dehydration due to

reduction in TBW relative to the concentrations of Na^+ and K^+ in the above equation with resultant increase in P_{osm} . In addition, adaptive response by brain cells to the changes in P_{osm} begins prior to admission and it involves accumulation of electrolytes (Na^+ and K^+), amino acids and idiogenic osmoles in the CNS [54,55]. Therefore, increased P_{osm} and adaptive CNS changes occurs prior to admission for DKA as a result of ongoing metabolic derangements typical of this condition. However, a drop in P_{osm} post-admission could result from alteration in the

ratio of $\text{Na}^+ + \text{K}^+/\text{TBW}$ as a result of therapy with fluid and insulin (**Table 4**), thus setting the stage for complications like CE-DKA. In the study by Hoorn *et al.* [56], a drop in P_{osm} occurred in 12 patients with CE-DKA who received and retained more fluid compared to controls. The CE-DKA patients in their study also had significantly lower levels (<135 mEq/L) of serum sodium (S_{Na^+}) before onset of treatment. Reviewing their study, Sema *et al.* [57,58] suggested that low pre-treatment S_{Na^+} is dilutional due to water retention from osmotic effects

Table 2. Laboratory abnormalities on admission for diabetic ketoacidosis.

Test	Comments
Plasma glucose	Usually >13.9 mmol/L (250 mg/dL): causes osmotic diuresis; glucose level drops with insulin and fluid therapy
Blood gas analysis (venous or arterial pH)	Metabolic acidosis usually present with $\text{pH} \leq 7.2$ in severe DKA
Bicarbonate	<15 mM: always reduced in DKA except in DKA complicated by metabolic alkalosis following exogenous bicarbonate therapy; only in this instance will serum bicarbonate concentration exceed 15 mM
Serum ketones	Usually 7 - 10 mmol/L in DKA. The nitroprusside reagent (Ketostix, Acetest) does not react with β -hydroxybutyrate; color reaction is mostly ($>80\%$) due to acetoacetate
Anion gap	Usually >15 in DKA; Δ Anion gap equals measured anion gap minus normal anion gap; ΔHCO_3 equals normal serum HCO_3 minus measured serum HCO_3 ; ratio of Δ anion gap/ ΔHCO_3 is usually less than unity; Δ anion gap/ ΔHCO_3 above unity signifies severe acidosis
Sodium	Low, normal or high: body stores are usually depleted; concentration depends on blood glucose and relative water loss.
Potassium	Low, normal or high: Body stores are depleted. Fatal hypokalemia could result from insulin therapy in the setting of hyperglycemia
Phosphate	Decreases with insulin therapy and volume repletion
^a BUN, creatinine	BUN and creatinine are usually high due to dehydration and decrease renal perfusion; BUN may better reflect renal function since creatinine may be spuriously high from cross reaction with acetoacetate
^b WBC count	Usually high but not indicative of infection; could be associated with lymphopenia and eosinopenia
^c Hb, ^d Hct, total protein, ^e SGOT, ^f SGPT, ^g LDH, ^h CPK	Hb, Hct & total protein are increased due to volume depletion; elevated CPK may be related to phosphate depletion and possible rhabdomyolysis
Amylase	Isoenzyme evaluation reveals that origin is pancreas (50%), salivary glands (36%) and mixed (14%) of cases

^aBUN, blood urea nitrogen; ^bWBC count, white blood cell count; ^cHb, hemoglobin; ^dHct, hematocrit; ^eSGOT, serum glutamic oxaloacetic transaminase; ^fSGPT, serum glutamic pyruvic transaminase; ^gLDH, lactate dehydrogenase; ^hCPK, creatine phosphokinase; Adapted with kind permission from Springer Science + Business Media, B. V. Adroque *et al.* [40].

Table 3. Ratio of excess plasma anion gap over bicarbonate deficit in diabetic ketoacidosis.

^a $\Delta\text{AG}/\Delta\text{HCO}_3$	Pre- and post-admission causes of changes in $\Delta\text{AG}/\Delta\text{HCO}_3$	Clinical findings on admission
Increase above unity	Vomiting Renal acid excretion Hyperproteinemia Exogenous bicarbonate therapy Tissue titration (Na^+/H^+ exchange)	Severe ECF volume deficit Major impairment of renal function Higher values of ^b Hct, ^c Hb, serum proteins, ^d BUN, creatinine, uric acid
Decrease below unity	Renal excretion of sodium salts of ketones Chloride containing infusions Hypocapnia induced suppression of ^e HCO_3 reabsorption Renal tubular acidosis	Mild ECF volume deficit Minor impairment of renal function Lower values of Hct, Hb, serum proteins, BUN, creatinine, uric acid

^a $\Delta\text{AG}/\Delta\text{HCO}_3$; ΔAG (mEq/L) equals measured anion gap (AG) minus normal AG; ΔHCO_3 , equals normal plasma bicarbonate minus measured plasma bicarbonate; expected value of this ratio is 1.0 since the bicarbonate deficit is the result of its titration by ketoacids; ^bHct, hematocrit; ^cHb, hemoglobin; ^dBUN, blood urea nitrogen; ^e HCO_3 , bicarbonate; Adapted with kind permission from Springer Science + Business Media, B. V. Adroque *et al.* [40].

Table 4. Factors associated with changes in effective serum osmolality (P_{osm}) before and after therapy in diabetes ketoacidosis.

Increased water loss & reduced intake (increased P_{osm})	Decreased plasma solute concentration (decreased P_{osm})
Vomiting	Decreased plasma glucose from insulin therapy and fluid administration (dilutional hypoglycemia)
Osmotic diuresis	Decreased serum potassium (movement of potassium into cells) with insulin therapy
Decreased renal concentrating ability due to hypokalemia and glycosuria	Decreased plasma sodium concentration from fluid and insulin therapy
Inability to access drinking water due to ^a CNS depression (younger aged children)	Increased excretion of solutes (glucose, ketoacids, sodium and potassium) as renal clearance improves (increased ^b GFR) with volume repletion

Effective plasma osmolality (P_{osm}) is determined by the ratio of exchangeable sodium (Na^+) and potassium (K^+) to total body water (TBW). These variables, $Na^+ + K^+/TBW$ (mEq/L) can be altered by concentration of sodium relative to free water administered. Increasing Na^+ content of administered fluid elevates P_{osm} by increasing plasma Na^+ concentration; increasing TBW decreases P_{osm} by decreasing plasma Na^+ concentration. Use of isotonic fluid has no effect on P_{osm} as ratio of Na^++K^+/TBW remains unchanged. ^aCNS, central nervous system; ^bGFR, glomerular filtration rate.

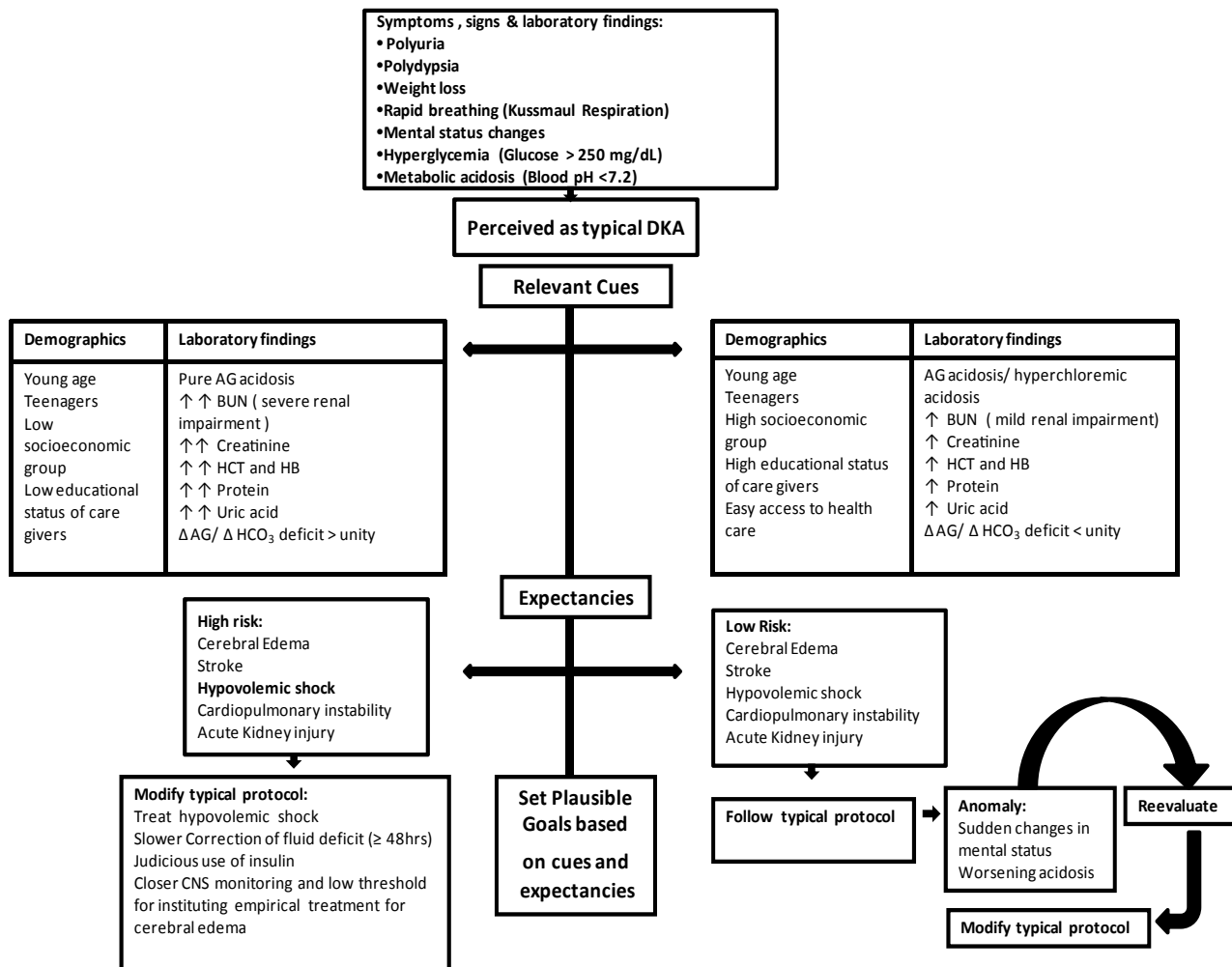


Figure 3. Pattern recognition of severity of DKA based on indices of renal function and other laboratory findings on admission. A pattern of relevant cues and expectancies can guide the clinician in setting plausible therapeutic goals. The algorithm shows the dynamic nature of clinical decision making in a complex metabolic disease like diabetic ketoacidosis.

of retained ketoacids and hyperglycemia in DKA patients with low GFR and reduced clearance of ketoacids and blood glucose. Thus DKA patients with renal insufficiency and severe metabolic acidosis on admission are at higher risk of CE-DKA from reduction in P_{osm} at commencement of therapy. Also, a drop in P_{osm} can result from the net reduction in ECF K^+ resulting from insulin therapy and kaliuresis as GFR improves following fluid repletion: movement of K^+ out of cells leads to a corresponding movement of Na^+ into cells, with the attendant drop in plasma Na^+ ultimately leading to reduced P_{osm} and osmotically mediated CNS swelling [59,60]. Also, the activation of Na^+-H^+ exchanger with insulin therapy (**Figure 3**) has been linked to changes in P_{osm} because insulin causes translocation of H^+ from ICF into ECF and a corresponding movement of Na^+ from ECF into ICF compartment to maintain electroneutrality; thus, CE-DKA could result from reduction in ECF Na^+ concentration and drop in P_{osm} at beginning of insulin therapy [61-64]. However, recent data from the study by Glaser *et al.* [65] did not show any association between onset of CE-DKA and osmotic fluctuations from therapeutic interventions because neither the rates of fluid, sodium and insulin administration, nor changes in serum glucose were associated with CE-DKA in their study; only a higher BUN, severe hypocapnia (marker of renal impairment and AG acidosis) at presentation and a slow rise in serum sodium (S_{Na^+}) after therapy were associated with CE-DKA in their study [65]: Glaser *et al.* [65] attributed absence of post-treatment rise in S_{Na^+} to CNS salt wasting rather than to dilutional hyponatremia from hyperglycemia or excessive fluid administration. Regardless of the cause, a low glucose corrected S_{Na^+} on admission and failure of S_{Na^+} to rise after correction of hyperglycemia with insulin have been identified as a central mechanism in the development of CE-DKA [57-66]. Rapid correction of fluid deficits may precipitate or worsen existing CNS injury in DKA, especially in late presenters with severe hyperosmolar dehydration and renal insufficiency [67,68]; therefore, correction of estimated fluid deficits should be accomplished slowly over 48 hours or longer as in cases of non-diabetic hyperosmolar dehydration and renal failure, once hypovolemic shock is corrected [67,68].

3. Conclusion

The pattern of acid-base and electrolyte disorders in DKA, patient's age, duration of symptoms and the degree of renal insufficiency prior to admission are important considerations in the evaluation and management of patients. Fluid therapy goals in pediatric DKA should be dictated by the degree of renal impairment and the severity of metabolic acidosis as determined by the ratio of excess AG to that of bicarbonate deficit on admission

[Figure 3].

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