Adv Exp Med Biol - Advances in Internal Medicine (2020) 4: 85–114
https://doi.org/10.1007/5584_2020_545

Published online: 3 Jun 2020

Acute Metabolic Emergencies in Diabetes: DKA, HHS and EDKA

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Abstract

Emergency admissions due to acute metabolic crisis in patients with diabetes remain some of the most common and challenging conditions. DKA (Diabetic Ketoacidosis), HHS (Hyperglycaemic Hyperosmolar State) and recently focused EDKA (Euglycaemic Diabetic Ketoacidosis) are life-threatening different entities. DKA and HHS have distinctly different pathophysiology but basic management protocols are the same. EDKA is just like DKA but without hyperglycaemia. T1D, particularly children are vulnerable to DKA and T2D, particularly elderly with comorbidities are vulnerable to HHS. But these are not always the rule, these acute conditions are often occur in different age groups with diabetes. It is essential to have a coordinated care from the multidisciplinary team to ensure the timely delivery of right treatment. DKA and HHS, in many instances can present as a mixed entity as well. Mortality rate is higher for HHS than DKA but incidences of DKA are much higher than HHS. The prevalence of HHS in children and young adults are increasing due to exponential growth of obesity and increasing T2D cases in this age group. Following introduction of SGLT2i (Sodium-GLucose co-Transporter-2 inhibitor) for T2D and off-label use in T1D, some incidences of EDKA has been reported. Healthcare professionals should be more vigilant during acute illness in diabetes patients on SGLT2i without hyperglycaemia to rule out EDKA. Middle aged, mildly obese and antibody negative patients who apparently resemble as T2D without any precipitating causes sometime end up with DKA which is classified as KPD (Ketosis-prone diabetes). Many cases can be prevented by following 'Sick day rules'. Better access to medical care, structured diabetes education to patients and caregivers are key measures to prevent acute metabolic crisis.

Keywords

Anion gap · ARDS (Acute Respiratory Distress Syndrome) · Cerebral Oedema · CSII (Continuous Subcutaneous Insulin Infusion) · Fixed Rate Intravenous Insulin Infusion (FRIII) · Hypokalaemia · Osmolality · Variable Rate Intravenous Insulin Infusion (VRIII)

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1 Introduction

DKA and HHS are two similar yet in many ways different metabolic emergencies of diabetes are encountered in emergency departments. Hyperglycemia, despite being the common ground for both conditions, is different in magnitude for each emergency, being more severe in HHS. Ketoacidosis is the hallmark of DKA found mostly in T1D due to absolute insulin deficiency. In HHS, ketoacidosis is nominal unless a mixed variety, which is due to residual insulin sufficient to prevent ketosis. It was thought that DKA is specific condition for T1D and HHS for T2D but this does not hold anymore. More and more cases of DKA are being reported in T2D and HHS in T1D. Similarly, the characteristic age distribution of acute hyperglycemic emergencies is not valid anymore. It is also not uncommon to find out mixture of two entities presenting in same patient.

Both of these conditions require immediate hospitalization and therefore have negative impact on the economy of a country. DKA primarily affects T1D and may be the first manifestation in up to 25% of cases (Dabelea et al. 2014; Jefferies et al. 2015; Rewers et al. 2008). More recently, EDKA is being found in T1D and T2D patient on SGLT2i (Peters et al. 2015). So there should be high index of suspicion in an unwell person with diabetes without hyperglycaemia on SGLT2i and EDKA should be ruled out. Up to 42% of DKA hospitalisations are due to readmissions for DKA within 1 year (Edge et al. 2016). It is a matter of solace that DKA mortality rates have fallen significantly in last 20 years from 7.96% to less than 1% (Umpierrez and Korytkowski 2016) Unfortunately, the mortality rates are still higher in patients over 60 years old with comorbidities, in low-income countries and in non-hospitalised patients (Otieno et al. 2006). The recent updated mortality in HHS is around 5–16% globally (Umpierrez and Korytkowski 2016). This high mortality rates necessitates early diagnosis and effective prevention programmes. Cheaper insulin should be readily available globally (Greene and Riggs 2015). The most common cause of mortality is cerebral oedema in children and young adults. On the other hand, the main causes of mortality in adults and elderly with HHS are diverse and many. The major causes are severe hypokalaemia, cardiac dysrhythmia, severe hypoglycaemia, ARDS, pneumonia, ACS (Acute Coronary Syndrome) and sepsis (Wolfsdorf et al. 2018).

Efforts should be directed to decrease hospitalization rate and acute metabolic crisis of diabetes by introducing structured diabetes education and provision of better healthcare to less developed areas. There exist some subtle differences in management protocols of DKA, EDKA and HHS patients. The purpose of this review is to provide the latest insights of epidemiology, pathophysiology, management and prevention of acute metabolic emergencies of diabetes.

2 Classification and Diagnostic Criteria

History, clinical examination, signs & symptoms and biochemical tests are required to aid diagnosis of condition. The classical triad of DKA includes hyperglycemia, ketonaemia and high anoin gap metabolic acidosis. The biochemical criterion set by JBDS, BSPED and ISPAD for diagnosis of DKA (Dhatariya 2014; Wolfsdorf et al. 2018; BSPED 2020) are as follows:

- Ketonaemia (blood level > 3 mmol/l) or ketonuria (2+ on dipstick)
- Hyperglycemia (>11 mmol/l) or known diabetic patient)
- Acidosis (HCO_3^- < 15 mmol/l and/or venous pH <7.3)

Classification of DKA is generally based upon anion gap, HCO_3, pH and cognitive status of patient.

Table 1 Classification of DKA in adults and children (BSPED 2020; Kitabchi et al. 2009; Sheikh-Ali et al. 2008; Kelly 2006).

Table 2 ADA, JBDS and AACE/ACE diagnostic criteria of DKA (Karslioglu French et al. 2019). The table is reproduced with permission.

Table 1 Classification of DKA in adults and children

Variables	Mild	Moderate	Severe
Blood glucose	Adult: >13.9 mmol/L (> 250 mg/dL)		
	Children: >11 mmol/L (> 200 mg/dL)		
Vitals (Pulse, SBP, SpO_2)	P < 100 or > 60 bpm, SBP >100; SpO_2 > 95%	P < 100 or > 60 bpm, BP >100; SpO_2 > 95%	P > 100 or < 60; BP <90; SpO_2 < 92%
Anion gap (mEq/L; mmol/L)	>10	>12	>16
Dehydration	5%	> 5 to 7%	>7 to ≥10%
Venous pH[a]	Adult: 7.24 to 7.3	Adult: 7.00 to <7.24	Adult: <7.00
	Children: 7.2 to 7.29	Children: 7.1 to 7.19	Children: <7.1
Serum osmolality mOsm/kg	Variable	Variable	Variable
Mental status	Alert	Alert/ drowsy	Stupor/ coma
Venous HCO_3[b]	Adult: 15 to 18	Adult: 10 to <15	Adult: < 10
(mEq/L, mmol/L)	Children: < 15	Children: < 10	Children: < 5
Serum/capillary BOHB[c] (mmol/L)	≥ 3.8 to <6 in adults; ≥ 3 to <6 in children	≥ 3.8 to <6 in adults; ≥ 3 to <6 in children	≥ 6 both adult and children
Urine STICKS-AcAc[d]	> 2+ in urine sticks	> 2+ in urine sticks	> 2+ in urine sticks
GCS	14–15	14–15	< 12

[a]Venous pH: just 0.02–0.15 units higher than arterial; [b]venous HCO_3: just 1.88 mmol/L lower than arterial; [c]BOHB: 3 β-hydroxybutyrate found in blood mainly; [d]*AcAc* acetoacetate found in urine mainly

Table 2 Diagnostic criteria of DKA in adults

Criteria	ADA	JBDS	AACE/ACE
Publication year	2009	2013	2016
Plasma glucose	>13.9 mmol/L	>11 mmol/L	NA
	(250 mg/dL)	(>200 mg/dL) or known diabetes	
pH	Mild: 7.25–7.30; moderate: 7.00–7.24; severe: <7.00	Mil & moderate <7.3 Severe: <7.0	<7.3
Bicarbonate, mmol/L or mEq/L	Mild: 15–18; moderate: 10–14.9; severe: <10	<15 but >5 Severe: <5	NA
Anion gap: Na^+–(Cl^- + HCO_3^-)	Mild: >10; moderate: >12; severe: >12	Mild & moderate >10 but <16 Severe: >16)	>10
Urine acetoacetate (nitroprusside reaction)	Positive	Positive	Positive
Blood BOHB, mmol/L	NA	Mild & moderate ≥3 Severe: >6	≥3.8
Mental status	Mild: alert; moderate: alert or drowsy; severe: stupor or coma	NA	Drowsy, stupor, or coma

The diagnostic criteria of DKA differs in many ways between societies. There is no consensus on all four key parameters such as ketonaemia/ ketonuria, HCO_3, pH and glucose values. Table 2 shows the diagnostic criteria formulated by key societies of diabetes.

JBDS criterion to classify severe DKA is slightly different and includes both physical and biochemical parameters.

Table 3 Diagnostic criteria of HHS by ADA and JBDS (Karslioglu French et al. 2019), reproduced with permission.

For DKA the prominent biochemical features are ketonemia and high anion gap acidosis. In HHS the circumstances are different as this condition is characterized by high osmolality and severe dehydration secondary to severe hyperglycemia. However in clinical practice, a mixed

Table 3 Diagnostic criteria of HHS in adults

Criteria	ADA	UK
Publication year	2009	2015
Plasma glucose	> 33.3 mmol/L (600 mg/dL)	≥30 mmol/L (540 mg/dL)
pH	>7.30	>7.30
Bicarbonate	>18 mmol/L	>15 mmol/L
Anion gap: Na^+–(Cl^- + HCO_3^-)	NA	NA
Urine acetoacetate (nitroprusside reaction)	Negative or low positive	NA
Blood BOHB	NA	<3
Osmolality, mmol/kg	>320	≥320
Presentation	Stupor or coma	Severe dehydration and feeling unwell

Table 4 Key differences between DKA, HHS AND EDKA

Variables	DKA	HHS	EDKA
Predominant feature	Ketonemia and high anion gap metabolic acidosis	Very high glucose and serum osmolality	Ketonemia and high anion gap metabolic acidosis
Glucose level mmol/L (mg/dL)	High: >13.9 (> 250)	Very high: ≥ 33.3 (≥600)	Normal: <11 (<200)
Ketones mmol/L	High (>3 mmol/L in blood or 2+ in urine)	Normal	High (>3 mmol/L in blood or 2 + in urine)
Serum osmolality mOsm/kg	Raised	> 320	Raised
Predominant diabetes type and comorbidities	T1D, less frequently in T2D and GDM	T2D, less frequently in T1D, T2D in children and in 6q24 genotype TND[a]	T1D, LADA, T2D on SGLT-2i, with pregnancy, glycogen storage disease, alcoholism, very low calorie diet, severe liver diseases etc.
Age	Young patient	Older patient	Mostly young patients but adults might also have
Predominant phenotype	Lean	Obese	Lean to obese
Complications	.7–10% risk of cerebral oedema, iatrogenic hypoglycaemia, hypokalaemia, ARDS and a small risk of arterial or venous thromboembolism	Iatrogenic hypoglycaemia, hypokalaemia, MI, DIC, higher risk of pulmonary, arterial or venous thromboembolism	Same like DKA

[a]*TND* transient neonatal diabetes

picture of DKA and HHS can also be encountered. It is also important to remember that some degree of acidosis in HHS can also be found due to nominal ketogenesis in some cases.

Table 4 Differences between DKA, HHS and EDKA (Rosenstock et al. 2018; Dandona et al. 2018; Mathieu et al. 2018; Blau et al. 2017; Rosenstock and Ferrannini 2015).

Euglycaemic DKA (EDKA/euDKA) was first reported in 1973 (Munro et al. 1973). It should be suspected in any diabetes patients who is on SGLT2i with classic symptoms. Diagnosis can be made with the classical cutoff level of pH, HCO3 and ketone with normoglycaemia (Dhatariya 2016). Many studies have shown evidence that use of SGLT2i in T1D and in LADA cases have higher incidence of EDKA. In advanced T2D there are few case reports published recently (Rosenstock and Ferrannini 2015). Reduced carbohydrate intake, depleted glycogen reserve due to alcoholism, SGLT2i in T1D, reduction of insulin might precipitate EDKA.

Ketosis-Prone Diabetes (KPD) KPD also called 'Flatbush diabetes' is found in certain ethnic minorities like African-Americans, Asians, sub-Saharan Africans and African-Caribbean. The genotype looks like idiopathic T1D but phenotype looks like T2D. Usually a middle aged obese man presents with DKA at diagnosis of new onset diabetes. Initial aggressive insulin therapy settles the acute stage. Subsequently, diet alone or a combination with oral hypoglycaemics can achieve glycaemic without need of insulin (Lebovitz and Banerji 2018). There are four types of classification of KPD such as 'ADA', 'modified ADA', 'BMI based' and 'Aβ' exist.

KPD classification 'Aβ' is based on the presence/ absence of autoantibodies and the presence/ absence of β-cell functional reserve. This is the most used and the most acceptable classification. The four subgroups are:

1. **A + β −** (present autoantibodies but absent β-cell function)
2. **A + β +** (present autoantibodies but present β-cell functional reserve)
3. **A − β −** (absent autoantibodies and absent β-cell function) and
4. **A − β +** (absent autoantibodies but present β-cell functional reserve).

A + β − and A − β − patients are immunologically and genetically distinct from each other but they share clinical characteristics of T1D with very low β-cell function. Whereas, A + β + and A − β + patients are immunologically and genetically distinct from each other but they share clinical characteristics of T2D with preserved β-cell functional reserve. Group 4 has the largest share of KPD with 76% (Balasubramanyam et al. 2006).

3 Epidemiology

DKA is no more considered as a metabolic emergency of only T1D (Bedaso et al. 2019; Jabbar et al. 2004; Takeuchi et al. 2017; Mudly et al. 2007). It is estimated that out of all DKA cases, around 34% occur in T2D (Kitabchi et al. 2009). Up to 25–40% cases of T1D present as DKA at first diagnosis (Duca et al. 2017). Apart from key precipitating factors, socio-economic factors also act as a causative factor of DKA. These are low income, limited access to health care facilities and illiteracy (Dabelea et al. 2014).

Desai et al. made a very large retrospective observational study that included 56.7 million hospitalisations during 2007–2014 with diabetes out of which 0.9% had DKA and HHS. Younger patients show (Fig. 1) highest rate of admissions with lowest mortality and the trend is reverse for older patients (Desai et al. 2019). According to a survey in USA, more than two-thirds of children presenting with HHS have T1D (Ng et al. 2020). These are mostly obese T1D and adolescent T2D.

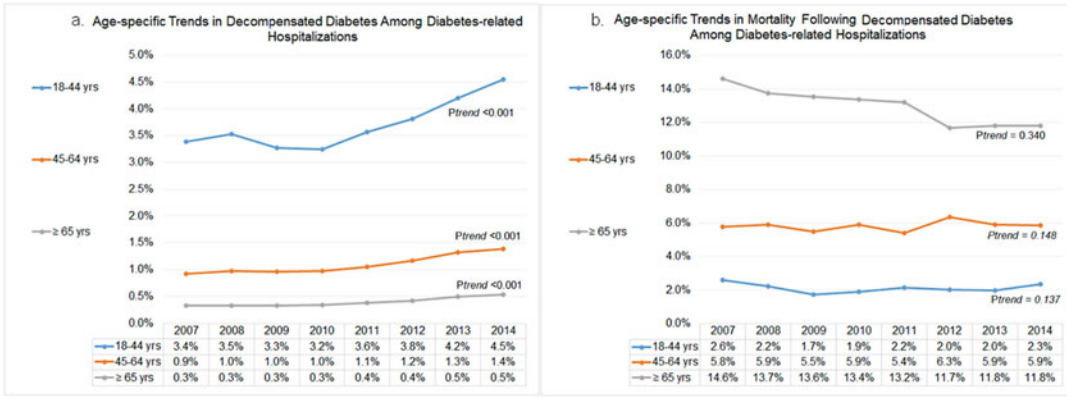

Fig. 1 Age-specific prevalence and morality of DKA and HHS (Desai et al. 2019). The figure is reproduced with permission

Table 5 SGLT2i use and EDKA rates in T1D

Studies	SGLT2i Molecule	Drug ARM	Placebo ARM	Event Rate/1000 PT YR
'EASE' Trial	Empagliflozin 2.5 mg, 10 mg and 25 mg	0.8%, 4.3% and 3.3%	1.2%	59.4, 50.5 and 17.7 events respectively
DEPICT-1 & 2 52-wk & 24-wk study	Dapagliflozin 5 mg and 10 mg	2.6% and 4% for 5 mg; 2.2% and 3.4% for 10 mg	1.9% (21.5 events/ 1 K patient yr)	58.3 and 47.6 events respectively
TANDEM-1 & 2 study	Sotagliflozin 200 mg and 400 mg	2.3%–3.4% for 200 mg and 3%-3.4%	0–0.6% (0–3.8 events/1 K patient year)	30–34 events
'FEARS' DATA	SGLT2i: Canagliflozin, Empagliflozin, Dapagliflozin	CANA-48 cases, DAPA-21 cases, EMPA-4 cases	N/A	Overall: 14-fold increase of DKA out of which 71% EDKA

From Prospective Diabetes registry in Germany comprising 31,330 patients, DKA admission rate was 4.81/100 patient-years (Karges et al. 2015). A multinational data from 49,859 children with T1D across three registries and five nations found higher odds of DKA in females (OR 1.23), in ethnic minorities (OR 1.27) and in those with HbA1c $\geq$ 7.5% (OR 2.54) (Maahs et al. 2015).

Table 5 Studies on SGLT2i in T1D with EDKA incidences (Rosenstock et al. 2018; Mathieu et al. 2018; Blau et al. 2017).

The hospitalization rate of HHS is less compared to DKA. According to an estimate it accounts for only 1% of diabetes related hospitalizations. In contrast to DKA, the mortality rate in HHS is considerably higher. It is 15% for HHS compared to 2–5% for DKA (Umpierrez et al. 2002). The possible explanations for this higher mortality rate for HHS are older age and presence of co-morbid conditions (Kitabchi et al. 2009).

4 Pathophysiology

4.1 DKA

Glucose homeostasis is maintained by the intricate balance of two hormones, insulin and glucagon. There are four axes (Fig. 2) which control glucose homeostasis. These are 'Brain-islet axis', 'Liver-islet axis', 'Gut-islet axis' and 'Adipocytes/ myocytes-islet axis'. These axes interplay with positive and negative feedback to maintain glucose homeostasis (Röder et al. 2016).

In DKA this hormonal balance of body is tilted towards counter-regulatory hormones due to absolute insulin deficiency. Due to this shift in balance, while liver uninhibitedly keeps on producing more glucose, peripheral tissues are not able to utilize glucose from blood in the absence of insulin (Gosmanov and Kitabchi 2000). The liver is able to secrete high amounts of glucose due to presence of two metabolic pathways namely gluconeogenesis and glycogenolysis. The gluconeogenic enzymes fructose 1, 6 bisphosphatase, phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase, and pyruvate carboxylase are mainly involved. These are stimulated by an increase in the glucagon to insulin ratio and by an increase in circulating cortisol concentrations (DeFronzo and Ferrannini 1987; Stark et al. 2014). This insulin counterregulatory hormone mismatch activates hormone sensitive lipase activity which leads to increase formation of FFAs from the triglycerides (Fig. 3). This FFAs are then beta oxidised to form acetylcoenzyme A into AcAc (Acetoacetic acid) and BOHB (Beta hydroxybutyrate) in hepatic mitochondria. These are major ketone bodies, resulting ketonemia and acidosis (Dhatariya 2016; Barnett and Barnett 2003).

Ketogenesis Conversion of FFAs into ketones in the hepatic mitochondria needs certain conditions. These are lower insulin to glucagon ratio, reduction

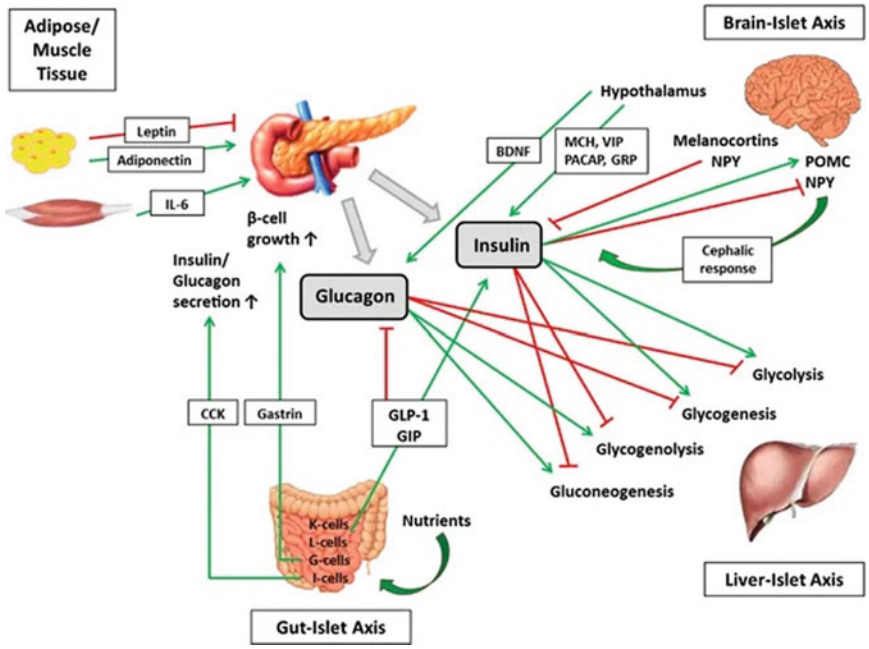

Fig. 2 Interplay of pancreas with brain, liver, gut, adipose and muscle tissue to maintain glucose homeostasis (Röder et al. 2016). The figure is reproduced with permission

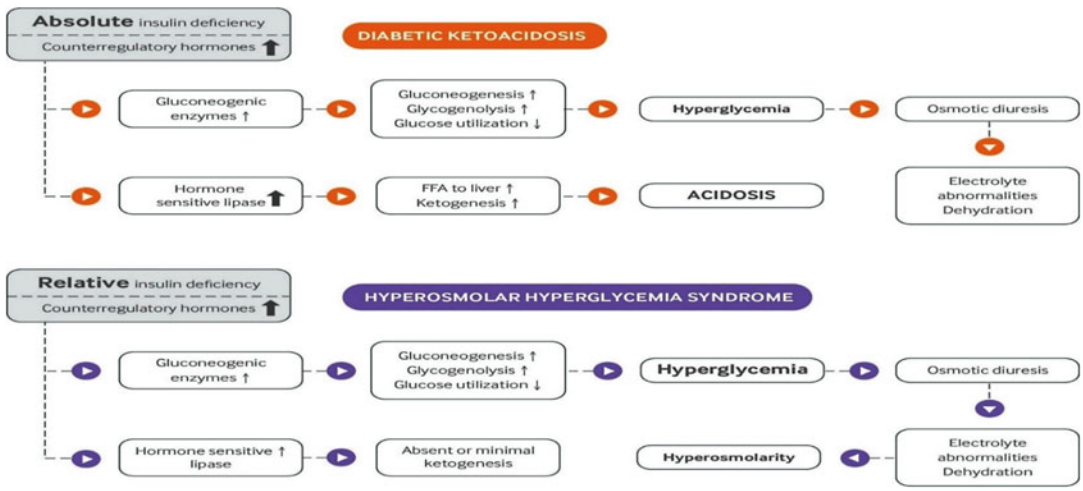

Fig. 3 Pathogenesis of DKA and HHS. Reproduced with permission (Karslioglu French et al. 2019)

in activity of acetyl CoA carboxylase and low levels of malonyl CoA. These eventually trigger transportation of FFAs inside mitochondria by CPT-1 (Carnitine Palmitoyltransferase-1) for conversion to ketones. FFAs in hepatic mitochondria are then broken down into acetyl CoA by beta-oxidation. Two acetyl-CoA molecules are converted into acetoacetyl-CoA by enzyme thiolase. Then this acetoacetyl-CoA is converted into HMG-CoA by HMG-CoA synthase. Then HMG-CoA is converted into acetoacetate by HMG-CoA lyase. Acetoacetate then converted into either acetone through nonenzymatic decarboxylation or into BOHB by beta-hydroxybutyrate dehydrogenase. In extra-hepatic

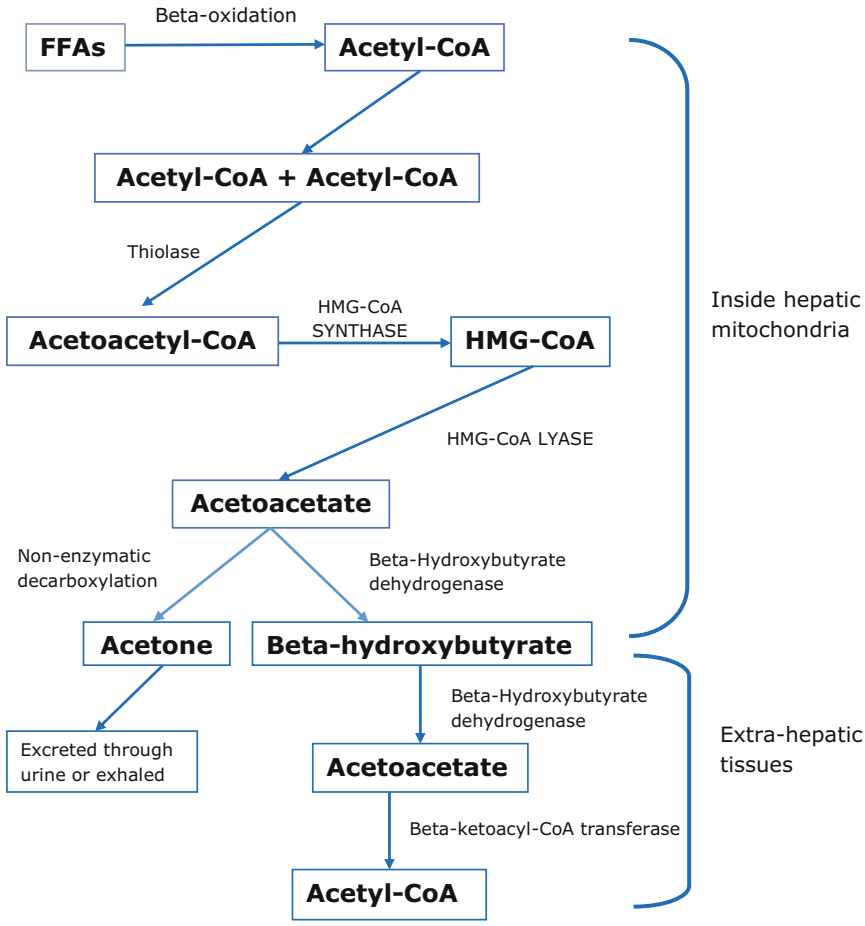

Fig. 4 Metabolic pathways of ketogenesis

tissues acetone is either excreted via urine or exhaled and BOHB is converted into acetoacetate by beta-hydroxybutyrate dehydrogenase. This end product acetoacetate is converted back to Acetyl CoA by beta-ketoacyl-CoA transferase (Fig. 4). This way ketogenesis continues till intervention is done (Dhillon and Gupta 2019). They are preferred over glucose in absence of insulin by many peripheral tissues like brain, and skeletal muscles (Barnett and Barnett 2003; Dhillon and Gupta 2019).

Acidosis As the concentration of Acetoacetic acid and β-hydroxybutyric acid increases in blood, they dissociates completely at physiological pH converting into acetoacetate and β-hydroxybytyrate respectively. This conversion yields hydrogen ion with each molecule which is at normal physiological state buffered by bicarbonate. In DKA the enormous amount of hydrogen ion forms due to ketogenesis. At one point bicarbonate buffering system fails and hydrogen ion concentration shoots up leading to falling blood pH and low bicarbonate (Dhatariya 2016; Barnett and Barnett 2003). The increased serum levels of glucose and ketones contributes towards osmotic diuresis and hence electrolytes disturbances and dehydration (Karslioglu French et al. 2019).

4.2 HHS

The pathogenesis of HHS differs from DKA significantly. Measurable insulin in T2D is higher than in DKA patients, which is sufficient to

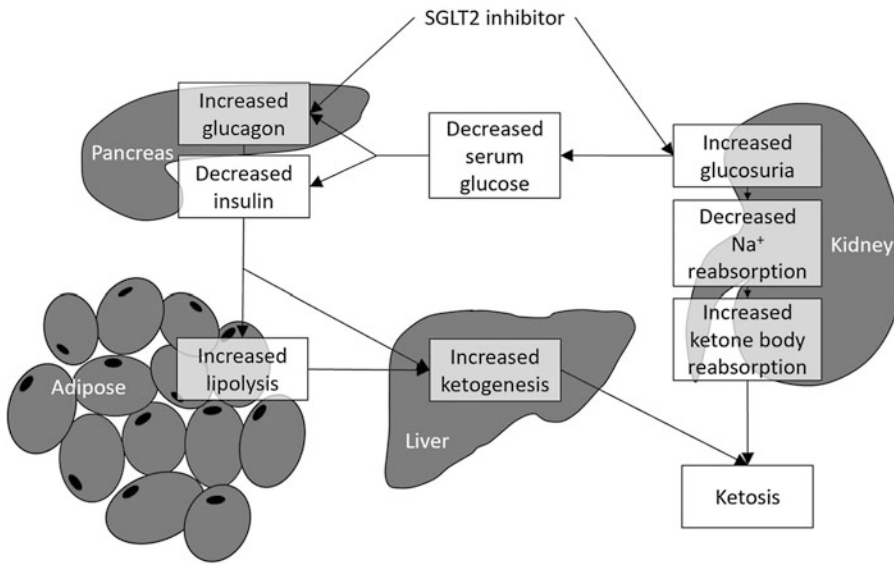

Fig. 5 Mechanism of development of EDKA with SGLT2i (Diaz-Ramos et al. 2019). The slide is reproduced with permission

suppress lipolysis and ketogenesis but inadequate to regulate hepatic glucose production and promote peripheral glucose utilization. Studies have shown the half-maximal concentration of insulin for anti-lipolysis is lower than for glucose utilization by peripheral tissues (Pasquel and Umpierrez 2014; Miles et al. 1983; Umpierrez et al. 1996). The counter-regulatory hormones are high in HHS due to presence of stresses like infection, and myocardial infarction. The reason behind more severe dehydration and hyperglycemia in HHS is that it develops over several days of continued osmotic diuresis. This leads to hypernatremia, especially in older patients with renal impairment. This is worsened by inability to drink adequate water to keep up urinary losses resulting in profound dehydration. Furthermore, this hypovolemia deteriorates glomerular filtration rate as clinically shown by higher creatinine values in HHS and it eventually leads to severe hyperglycaemic state (Umpierrez et al. 2002; Kitabchi et al. 2006).

4.3 EDKA

In T2D on SGLT2i, the lower insulin to glucagon ratio stimulates lipolysis which makes around 20% enhanced lipid oxidation. This happens at the expense of markedly reduced carbohydrate oxidation, which falls by 60%. In the face of lower glucose concentrations, nonoxidative glucose disposal by glycogen synthesis and lactate release also fall by 15% (Rosenstock and Ferrannini 2015). Reduced insulin level causes reduced formation of acetyl-CoA, so inhibition of CPT-I is less. This promotes transport of FFAs into mitochondria and hence ketogenesis (Diaz-Ramos et al. 2019). BOHB levels rises by two folds in fasting and fed state. Plasma lactate level decreases to 20% which reflects reduced carbohydrate utilization. In T1D where absolute insulin deficiency prevails and if carbohydrate availability is drastically reduced then the mild ketosis would lead to ketoacidosis (Rosenstock and Ferrannini 2015) (Fig. 5).

5 Precipitating Factors

The predominant trigger for an acute DKA episode is insulin omission or non-adherence, whereas in HHS infections are most common precipitating factors. In EDKA, there is common association with the use of SGLT2i which ensures good

Table 6 Precipitating factors of DKA, HHS AND EDKA

DKA	HHS	EDKA
Strong factors		
Reduction or repeated omission of insulin dose. Infection: most common are respiratory and UTI	Infections especially UTI and pneumonia in 30–60% cases	Reduction in insulin dose at the context of good glycaemic control in patients on SGLT2i
Non-compliance with insulin, poor control, h/o previous episode	Non adherence to insulin or oral antidiabetic medications	Reduction in carbohydrate intake
Gastroenteritis with persistent vomiting, dehydration. Binge alcohol intake, cocaine or substance abuse	Alcohol abuse, restricted water intake in nursing home residents with diabetes	Alcohol, cocaine or substance abuse
		Failure to stop SGLT2i prior surgery
Acute MI in middle aged T1D or T2D	Acute MI, CVA	Acute MI in middle aged T1D or T2D
Eating disorders, psychiatric disorders, parental abuse, peripubertal and adolescent girls	Depression	Eating disorders, psychiatric disorders
Weak factors		
Pancreatitis, CVA in elderly T1D or T2D, pregnancy	Post cardiac or orthopedic procedure where osmotic load is increased, pregnancy	Chronic alcoholism, pregnancy
Endocrine diseases: Acromegaly, hyperthyroidism, Cushing syndrome	Delay in insulin initiation postoperatively, TPN	Glycogen storage disease
Drugs: corticosteroids, thiazides, Pentamidine, sympathomimetics, second-generation antipsychotics, cocaine, immune checkpoint inhibitors	Drugs: corticosteroids, thiazides, beta-blockers, didanosine, phenytoin, Gatifloxacin, cimetidine, atypical antipsychotics-clozapine, olanzapine	
Remembering 7 'I' can be easy to remember the causes	1. **I**nsulin: Deficiency/insufficiency	5. **I**nfarction: ACS, stroke
	2. **I**atrogenic: Steroids, thiazides, atypical antipsychotic drugs	6. **I**nflammation: Acute pancreatitis, cholecystitis
	3. **I**nfection: Commonest cause	1.7. **I**ntoxication: Alcohol, cocaine
	4. **I**schaemia: Gut, foot	

glycaemic control that might lead to reduction in insulin dosage. These triggers higher secretion of counter-regulatory hormones in DKA, HHS and EDKA. Table 6: Precipitating factors in DKA, HHS and EDKA (Pasquel and Umpierrez 2014; Laine 2010; Adeyinka and Kondamudi 2020).

6 Clinical Presentation

DKA and EDKA evolve in hours to days but HHS develops gradually over several days to weeks. Results of a systematic review which included 24,000 children from 31 countries suggested that those who are very young and belong to ethnic minorities are more to present acutely in such manner. Other major risk factors include lean built of body, errors in diagnosis of T1D, treatment delays, infection as presenting complaint etc. Presence of T1D in family history, on the other hand, makes it unlikely that DKA would be the first presentation (Usher-Smith et al. 2011). Up to 25% patients with new-onset T1D present with DKA (Choleau et al. 2014; Jefferies et al. 2015; Usher-Smith et al. 2011).

Table 7 Features of clinical presentations of DKA, HHS and EDKA (BSPED 2020; Hardern 2003; Trence and Hirsch 2001; Hamdy 2019; Nyenwe et al. 2010; Usher-Smith et al. 2011).

In an otherwise healthy child without any family history of diabetes who presents as with urinary symptoms, it is challenging to diagnose T1D (Rafey et al. 2019). Up to 20% people present with HHS as first presentation of new-onset T2D (Pasquel and Umpierrez 2014). EDKA is difficult to diagnose without detail history and work-up as

Table 7 Clinical presentations of DKA, HHS AND EDKA

Parameter	DKA	HHS	EDKA
History	Short h/o unwellness, hours to days	Unwellness for days to weeks	Moderate length
	h/o failure to comply with insulin therapy	Often a preceding illness like dementia, immobility predisposes	h/o SGLT2i intake and not stopped prior surgery
	h/o mechanical failure of CSII		h/o alcoholism, poor carb intake
Most common early features	Polyuria, polydipsia and polyphagia	Polyuria, polydipsia	Lesser osmotic symptoms but other DKA features are present
	Nausea, vomiting and anorexia	weight loss, weakness, lethargy	
	loss of appetite, diffuse abdominal pain	Seizures which may be resistant to anticonvulsive and phenytoin may worsen HHS, muscle cramps	
	Malaise, generalized weakness, fatigue		
	Rapid weight loss in new-onset T1D	Uncommon: Abdominal pain	
Late features	Dry mucous membrane, poor skin turgor	Same as DKA but dehydration is profound	Same as DKA but dehydration is moderate
	Sunken eyes, hypothermia	Acute focal or global neurologic changes: drowsiness, delirium, focal or generalized seizures, coma, visual changes, hemiparesis, sensory deficits	
	Tachycardia, hypotension,		
	Kussmaul breathing, acetone breath, laboured breath, tachypnea		
	Altered mental status, reduced reflexes		
Features of possible intercurrent infection	Constitutional symptoms: fever, cough, chills, chest pain, dyspnea, arthralgia	Same as DKA and infectious components are most common precipitants in HHS	Same as DKA but very less frequently any infectious components are seen

there is usually very low index of suspicion with normoglycaemia.

7 Laboratory Investigations

The laboratory investigations in DKA, HHS and EDKA are aimed primarily for diagnosis and to determine its severity. Then the next step is to identify the underlying causes, early identification of complication and monitoring of response to therapy. As acute metabolic decompensation is an emergency so just after history, clinical examination and provisional diagnosis management starts. Blood and urine samples are taken to do initial investigations without delay. Work-up for DKA and EDKA are same. Table 8 Initial and subsequent work-ups in the management of DKA and HHS (Wolfsdorf et al. 2018; Savage et al. 2011; Scott et al. 2015; Khazai and Umpierrez 2020; Gosmanov and Nimatollahi 2020; Rawla et al. 2017).

8 Differential Diagnosis

The acute hyperglycemic emergencies DKA and HHS are at the top of differential list for each other. The only biochemical feature that differentiates DKA from EDKA is serum glucose level: normal in EDKA and raised in DKA. The distinguishing feature of HHS is presence of high serum osmolality due to extremely high serum glucose levels. The hyperglycemia in HHS is generally greater than 30 mmol/l (Scott et al. 2015; Westerberg 2013).

Table 8 Work-up for DKA, HHS and EDKA

Initial tests to order			
Tests	DKA results	HHS results	Comments
Plasma glucose	> 13.9 mmol/L (>250 mg/dL)	>33.3 mmol/L (>600 mg/dL)	Elevated except in EDKA it is <11 mmol/L (<200 mg/dL)
Venous blood gas	pH varies from 7.00 to 7.30	Usually >7.30	Venous pH is just 0.03 lower than arterial pH. As arterial sampling is painful and risky so venous sample is now commonly taken
Capillary or serum ketones	BOHB $\geq$3.8 mmol/L in adults and $\geq$ 3.0 mmol/L in children	BOHB is negative or low	Out of three ketones, BOHB (beta hydroxybutyrate) is early and abundant ketone that is checked first from serum or point-of-care device. In early DKA, acetoacetate (AcAc) can be measured, its result has a high specificity but low sensitivity. Acetone not done as it is volatile
$HbA1_c$ level	Usually high	Usually high	To evaluate the glycaemic control it is done but in good glycaemic control acute hyperglycaemic crisis may precipitate
Urinalysis	Positive for glucose and ketones. Positive for leukocytes and nitrites if there is an infection	Positive for glucose and but usually not ketones. Positive for leukocytes and nitrites if there is an infection	In mixed presentation of DKA and HHS urine ketone also found in HHS
Serum bicarbonate	From 18 mEq/L or mmol/L to <10 depending the grade	> 15 mEq/L	Bicarbonate is an important test to diagnose and grade
Serum bun	Increased due to dehydration	Markedly increased due to severe dehydration	Pre-renal azotaemia
Serum creatinine	Increased due to dehydration	Markedly increased due to severe dehydration	Once dehydration is corrected the creatinine level returns to normal
Serum sodium	Usually low	Variable, usually low but can be high	Total Na deficit in DKA is 7–10 mEq/kg and in HHS is 5–13 mEq/kg. Hypernatraemia with hyperglycaemia indicates profound dehydration
Serum potassium	Usually elevated	Usually elevated but decreased in severe cases	Total deficit of K in DKA is 3–5 mEq/kg and in HHS 4–6 mEq/kg. K is elevated initially due to extracellular shift caused by insulin deficiency or insufficiency, hypertonicity and acidaemia. Low K on admission is a sign of severe case
Serum chloride	Usually low	Usually low	Cl loss is 3–5 mEq/kg in DKA and 5–15 mEq/kg in HHS
Serum magnesium	Usually low	Usually low	Mg deficit is 1–2 mEq/kg in DKA and 0.5 to 1 mEq/kg in HHS
Serum calcium	Usually low	Usually low	Ca deficit is 1–2 mEq/kg in DKA and 0.5–1 mEq/kg in HHS
Serum phosphate	Normal or elevated	Usually low	1 mmol/L deficit in DKA but initially shows normal or elevated. After insulin therapy it decreases. In HHS 3–7 mmol/kg is lost due to diuresis

(continued)

Table 8 (continued)

Initial tests to order			
Tests	DKA results	HHS results	Comments
CBC	Usually elevated	Usually elevated	Leukocytosis correlates with ketones but >25,000/ microliter indicates infection and indicates further evaluations
LFT	Usually normal	Usually normal	Abnormal results due to fatty liver or congestive heart failure may be found
Serum amylase	Usually elevated	Usually elevated	In majority of DKA cases amylase is elevated but mostly due to nonpancreatic causes. In HHS if elevated then pancreatitis should be ruled out
Serum lipase	Usually normal	Usually normal	In elevated amylase level measuring lipase level is useful to differentiate pancreatitis
Serum osmolality	Variable	High, usually ≥320 mOsm/L	Twice measured Na and K plus Glucose makes the osmolality. Urea usually not counted as it is freely permeable. A linear relationship is there between effective osmolality and mental state in HHS. Neurological deficits begin above 320 and stupor or coma come above 340 mOsm/L
Additional tests to consider			
Chest X-RAY	May have findings of pneumonia	Variable, may be compatible with pneumonia	The commonest infections are pneumonia and UTI
ECG	May show findings of MI or hyperkalaemia or hypokalaemia	May show findings of MI or hyperkalaemia or hypokalaemia	Precipitating CAD and severe electrolyte abnormalities are common in both DKA and HHS
Cardiac biomarkers	In suspected MI should be done	In suspected MI should be done	Cardiac troponins are elevated in suspected MI
Body fluid culture	To rule out sepsis blood, urine or sputum culture are needed	To rule out sepsis blood, urine or sputum culture are needed	Fever, leukocyte count >25,000/ microliter should raise the question of infective focus
Creatinine phosphokinase	In cocaine abuse rhabdomyolysis is common	Less common	↑ In rhabdomyolysis. pH and serum osmolality mildly elevated. Blood glucose and ketone are normal. Myoglobinuria/ hemoglobinuria + in urine
Serum lactate	Normal if concomitant lactic acidosis absent	Normal if concomitant lactic acidosis absent	Elevated in lactic acidosis

Ketoacidosis besides being present in diabetes can also occur during starvation and alcoholism. It is important to rule out other causes of high anion gap acidosis like salicylate poisoning, methanol intoxication and lactic acidosis (Keenan et al. 2007). Since abdominal pain and vomiting episodes are often present in such patients, other etiological causes of acute abdomen like pancreatitis and gastroenteritis should also be considered in differential diagnosis (Keenan et al. 2007).

Due to presence of focal neurological deficit, HHS is very commonly confused with stroke (Umpierrez et al. 2002).

Table 9 Differential diagnosis of acute hyperglycaemic crisis (Westerberg 2013; Rawla et al. 2017; Keenan et al. 2007).

Table 9 Differential diagnosis of DKA, HHS and EDKA

Condition	Differentiating features	Tests to rule out
HHS	HHS patients are usually older and commonly with T2D. Symptoms evolve insidiously, more frequently mental obtundation and shows focal neurological signs. Blood glucose is very high in HHS whereas in EDKA it is normal, other distinguishing features are similar to DKA	Blood glucose >33.3 mmol/L, serum osmolality is >320 mOsm/kg and ketones are normal or mildly elevated. Anion gap is variable but usually <12 mEq/L, pH is >7.30 and bicarbonate is >15 mEq/L
DKA	DKA patients are younger and leaner T1D, usually present with abdominal pain and vomiting	pH < 7.30, HCO3 < 15 mmol/L, anion gap >12 mEq/L and ketones are strongly positive
Lactic acidosis	DKA and HHS like presentation but in pure form of lactic acidosis blood glucose and ketone are normal but lactate is raised. History of diabetes may not be there	In T1D with sepsis, lactic acidosis sometime precipitate. Bicarbonate, pH and anion gap are similar to DKA but lactic acid >5 mmol/L. Blood glucose and ketones are normal
Starvation ketosis	Starvation ketosis mimics partly with DKA. It is the consequence of prolonged inadequate availability of carbohydrate. Which results compensatory lipolysis and ketogenesis to provide fuel substrate for muscle	Blood glucose is normal or low, blood ketone is normal but urine contains huge amount of ketones. Blood pH is normal and anion gap is just mildly elevated
Alcoholic ketoacidosis	It results in chronic alcoholics who skips meals and depends on ethanol as main source of calorie for days to weeks. Ketoacidosis is triggered when alcohol and calorie intake abruptly decreases. Signs of chronic liver disease such as spider naevi, palmer erythema, leukonychia, easy bruising, jaundice and hepatomegaly might be present	There is mild to moderate metabolic acidosis with elevated anion gap. Serum and urine ketones are positive. There might be hypoglycaemia
Salicylate poisoning	History is crucial to differentiate. Salicylate poisoning results an anion gap metabolic acidosis with respiratory alkalosis	Salicylate is positive in blood and urine, blood glucose is normal or low, ketones are negative, osmolality is normal. Interestingly, salicylate makes false-positive and false-negative urinary glucose presence
Paracetamol overdose	History is very crucial to differentiate. Confusion, hyperventilation, tinnitus and signs of pulmonary oedema might be found	A positive result for serum and urine paracetamol could be found but might not be in toxic range. Blood sugar may be normal or low
Toxic substance ingestion	History is crucial to differentiate. Common toxic substances are methanol, ethanol, ethylene glycol and propylene glycol. Paraldehyde ingestion makes strong odour in breath	Serum screening for toxic substances might yield the clue. Calcium oxalate and hippurate crystals in urine indicate ethylene glycol ingestion. These organic toxins can produce anion gap and osmolar gap due to low molecular weight
Stroke	Symptoms develop rapidly, in seconds to minutes. There might be limb and facial weakness	Cranial CT or MRI is diagnostic
Uremic acidosis	High BUN and creatinine but normal glucose. A history also important	Very high serum creatinine and BUN are found

9 Management: General

Successful management of DKA, HHS and EDKA needs 5 major components to rectify as follows (Hamdy 2019):

1. Correction of dehydration
2. Correction of hyperglycaemia and ketoacidosis
3. Correction of electrolyte abnormalities
4. Identification of comorbid and precipitating factors and
5. Frequent monitoring and prevention of complications

Once acute metabolic crisis of diabetes is recognized the patient needs to be hospitalized in emergency or acute medical unit or in HDU (High Dependency Unit) or in ICU depending on grading.

Table 10 Markers of severity that requires HDU/ICU admission

Markers of severity	DKA/EDKA	HHS
Venous pH	pH < 7.1	< 7.1
Blood ketones	> 6 mmol/L	> 1 mmol/L
Serum bicarbonate, anion gap	< 5 mmol/L, > 16 mmol/L	
Potassium	< 3.5 mmol/L or > 6 mmol/L	< 3.5 mmol/L or > 6 mmol/L
Systolic BP, pulse	< 90 mmHg, >100 or < 60 bpm	< 90 mmHg, >100 or < 60 bpm
Urine output	< 0.5 mL/kg/h or evidence of AKI	< 0.5 mL/kg/h or evidence of AKI
Mental status, SpO_2	GCS <12 or abnormal AVPU, <92%	GCS <12 or abnormal AVPU, <92%
Sodium, osmolality		>160 mmol/L, >350 mOsm/kg
Comorbidities	Hypothermia, ACS, CHF or stroke	Hypothermia, ACS, CHF or stroke

Table 11 Typical water and electrolyte deficits in DKA, EDKA and HHS (Umpierrez et al. 2002; Savage et al. 2011; Scott et al. 2015)

Variables	DKA/EDKA (deficit/kg body wt)	HHS (deficit/kg body wt)
Water	100 ml	100–200 ml
Na^+	7–10 mEq	5–13 mEq
K^+	3–5 mEq	5–15 mEq
Cl^-	3–5 mEq	4–6 mEq
$PO4^-$	5–7 mEq	3–7 mEq
Mg^{2+}	1–2 mEq	1–2 mEq
Ca^{2+}	1–2 mEq	1–2 mEq

Table 10 The markers of severity in DKA, HHS and EDKA for HDU/ICU admission (Savage et al. 2011; Scott et al. 2015).

The markers of severity should be assessed and recorded (Table 11).

Management should start with prompt assessment of ABCDE (**A**irway, **B**reathing, **C**irculation, **D**isability-conscious level and **E**xposure-clinical examination) at emergency department. Acute metabolic crisis in diabetes leads to profound water and electrolyte loss due to osmotic diuresis by hyperglycaemia. In EDKA due to very nominal rise of glucose, water deficit is not profound like DKA but is significant due to ketoacidosis. Without finding the cause of acute metabolic crisis, the management is not complete. Without preceding a febrile illness or gastroenteritis, DKA in a known diabetes patient is usually due to psychiatric disorders such as eating disorders and failure of appropriately administering insulin (Wolfsdorf et al. 2018). Comparatively more aggressive fluid replacement in HHS is needed than DKA to expand intra and extra vascular volume. The purpose is to restore normal kidney perfusion, to normalize sodium concentration and osmolality. DKA usually resolves in 24 h but in HHS correction of electrolytes and osmolality takes 2–3 days. Usually HHS occurs in elderly with multiple co-morbidities, so recovery largely depends on previous functional level and precipitating factors. In EDKA if SGLT2i is suspected, it should be stopped immediately and should not restart unless another cause for DKA is found and resolved (Evans 2019).

9.1 Management: From Admission to 24–48 Hours

Table 12 Shows the details of management from admission onwards (Wolfsdorf et al. 2018; BSPED 2020; Savage et al. 2011; Scott et al. 2015; Evans 2019) (Fig. 6).

Table 12 Management of DKA, EDKA and HHS IN adults and children

	DKA, EDKA and HHS	
Intervention	0–60 min: Resuscitate, diagnose and treatment	Monitoring, ongoing lab work-up
ABCDE	Fast assessment to grade patient: Shocked, comatose, moderate or mild cases	**First tests:** CBC, U & E, and venous blood gas: pH, HCO3, CRP, glucose, ECG, CXR, infection screen if indicated by blood and urine culture
	In shocked and comatose patients with vomiting an airway, N/G tube have to insert	**HOURLY**: Capillary blood glucose, ketones, cardiac monitoring, BP, pulse, respirations, pulse oximetry, fluid input/output chart, neurological observations
	100% oxygen by face mask	
	IV cannula have to put and blood and urine sample have to take. Cardiac monitor with pulse oximetry have to attach to assess pulse, BP, T wave etc.	**TARGET:** Reduction of glucose by 3 mmol/L/h, ketones by 0.5 mmol/L/h and increasing HCO3 by 3 mmol/L/h
	Blood and urine sample to send for culture for infection screening	
	Elderly HHS patients are at high risk of pressure sore. Foot assessment should be done and should apply heel protectors in those with neuropathy, PVD or lower limb deformity	
Bedside diagnosis	Capillary blood test, point of care blood ketone test and if not available urine dipsticks for 15 s where a > ++ indicates positive	
	Comatose and shocked patients should move to HDU/ICU immediately after starting IV fluid	
	Use of blood gas machine at bedside can promptly test pH, urea, electrolytes, glucose etc. while first blood sample is sent to laboratory	
Initial fluid replacement	Crystalloid fluid such as normal saline is best for volume expansion rather than colloid fluid. Typical fluid deficit is 100 mL/kg and should be corrected within 24–48 h	
	All children with mild, moderate or severe DKA who are not shocked should receive an initial bolus of 10 mL/kg 0.9% NaCl IV over 60 min stat	
	Shocked children should get bolus of 20 mL/kg 0.9% NaCl IV over 15 min stat	
	The maintenance fluid in children should be calculated from Holliday-Segar formula. It is: 100 mL/kg/day for first 10 kg body weight, then 50 mL/kg/day for next 10 kg and 20 mL/kg/day for each kg above 20 kg. This amount should be divided by 24 to get hourly maintenance amount	
	A 5%, 7% and 10% fluid deficit is assumed for mild, moderate and severe DKA respectively. Initial bolus should be subtracted from deficit and then divided by 48 h and adding this to hourly maintenance fluid volume	

(continued)

Table 12 (continued)

Intervention	DKA, EDKA and HHS 0–60 min: Resuscitate, diagnose and treatment	Monitoring, ongoing lab work-up
	HOURLY RATE = [DEFICIT- INITIAL BOLUS] /48 + MAINTANANCE PER HOUR	
	Alert, not clinically dehydrated, no nausea or vomiting children do not always need IV fluids even their ketone is high. They might tolerate oral rehydration and s.c insulin but they do require continuous monitoring to ensure improvement and ketone is falling	
	Adult DKA, EDKA patients should get 1–1.5 L 0.9% NaCl saline in first hour. In DKA average 6 L fluid loss occurs. Slower administration in young, elderly, pregnant, heart and renal failure cases	
	Adult HHS patients should get 1–1.5 L 0.9% NaCl in first hour provided cardio-renal status allows. In HHS average 7–9 L fluid loss occurs	
Insulin therapy	Insulin should start immediately in DKA and HHS if potassium level is >3.3 mEq/L. A 50 units of soluble insulin (e.g. Actrapid) in 49.5 mL of 0.9% NaCl saline to be mixed to make 1 unit/mL to administer through infusion pump	
	Two types of insulin regimens are used in DKA and HHS. First one is fixed rate IV regular insulin infusion as known as **FRIII** (fixed rate intravenous insulin infusion) at 0.14 units/ kg/ h with no initial bolus. Second one is 0.1 units/kg/h IV bolus followed by FRIII at a rate of 0.1 units/kg/ h continuous IV infusion	
	In EDKA insulin infusion with 5–10% dextrose in saline helps to settle ketoacidosis	
	In young children with mild to moderate DKA 0.05 units/ kg/h is sufficient to control and in severe DKA and in adolescent patients 0.1 units/kg/h should start **after 1 h of fluid replacement therapy**	
	In children with HHS insulin need is less. So a dose of 0.025 to 0.05 units/kg/ h should start **after 1 h of fluid replacement**	
	Insulin pump should stop when FRIII is started. Long acting basal insulin should continue at the usual dose throughout the treatment, it helps to shorten the length of stay after recovery	
	If blood glucose does not fall by 10% or 3 mmol/L in first hour then a dose of	

(continued)

Table 12 (continued)

Intervention	DKA, EDKA and HHS 0–60 min: Resuscitate, diagnose and treatment	Monitoring, ongoing lab work-up
	0.14 units/kg of regular insulin should be given IV bolus and then to continue FRIII at running dose	
	Once blood glucose falls near 13.9 mmol/L (250 mg/dL), then insulin infusion should be reduced to 0.02–0.05 units/kg/h and a 5% dextrose in saline have to add while maintaining blood glucose 11–17 mmol/L (200–300 mg/dL)	
	Rapid reduction of blood glucose should be avoided to prevent sudden osmolar changes and cerebral oedema	
	Insulin injection by a sliding scale is no longer recommended	
Potassium replacement	In acute metabolic crisis in diabetes potassium loss is around 3–15 mEq/kg. Insulin therapy, correction of acidosis and hyperosmolality drive potassium into cells causing serious hypokalemia. So to prevent complications of hypokalemia like respiratory paralysis and cardiac dysrhythmia insulin therapy should be withheld if K level is <3.3 mEq/L at baseline while fluid therapy is going on	
	If K is >5.5 mmol/L = NO potassium	
	If K is 3.5–5.5 mmol/L = 20–40 mmol/L mixed with 0.9% NaCl saline	
	If K is <3.5 mmol/L = 40 mmol/L over 1–2 h with cardiac monitoring	
	Urine output of >50 mL/h should be there while patient on K therapy. The hydration status should be evaluated clinically regularly. If eGFR is <15 mL/min then consultation with renal team is needed before adding K	
	If K level falls <3.3 mEq/L in any time during therapy, insulin should be withheld and K 40 mmol/L should be added in each liter of infusion fluid	
Vesopressor and anticoagulant therapy	If hypotension persists after initial forced hydration, then a vasopressor agent should be administered. Dopamine or Noradrenaline can be used. Dopamine increases stroke volume and heart rate whereas Noradrenaline increases mean arterial pressure	
	Dopamine 5–20 micrograms /kg/min IV infusion, subject to adjustment as per response	
	Noradrenaline 0.5–3 micrograms/min IV infusion and titration as per response. Can be used maximum 30 micrograms/min	

(continued)

Table 12 (continued)

Intervention	DKA, EDKA and HHS 0–60 min: Resuscitate, diagnose and treatment	Monitoring, ongoing lab work-up
	Diabetes and hyperosmolality make increased risk of venous thromboembolism (VTE). It is similar to patients with acute renal failure, acute sepsis or acute connective tissue disease	
	The risk of VTE is greater in HHS than DKA. Hypernatraemia and increased antidiuretic hormone promote thrombogenesis	
	Patients with HHS who are at risk or suspected with thrombosis or ACS should receive prophylactic low molecular weight heparin (LMWH) during admission. There are increased risk of VTE beyond the discharge, so LMWH should continue for 3 months after discharge (Keenan et al. 2007)	
	1–6 Hour: Assessment and monitoring therapy	
Fluid Replacement Continues, FRIII Continues, K replacement if needed	0.9% NaCl 1 l over 2 h, then	**WORK-UP:** **2 HOURLY** serum K, HCO3, venous blood gas for pH **HOURLY**: Capillary blood glucose, ketones, cardiac monitoring, BP, pulse, respirations, pulse oximetry, fluid input/output chart, neurological observations
	0.9% NaCl 1 l over 2 h, then	
	0.9% NaCl 1 l over 4 h	
	After first hour therapy of 1–1.5 L if signs of severe dehydration such as orthostatic hypotension or supine hypotension, poor skin turgor etc. persists then 1 l per hour have to continue till signs resolved	
	These patients' when symptoms are resolved then continue to receive infusion fluid on the basis of corrected sodium	
	CORRECTED Na^+ = MEASURED Na^+ + (GLUCOSE in mmol/L- 5.6)/3.5	
	In hyponatraemic patients: 0.9% NaCl at 250–500 mL/h and when blood glucose reaches 11 mmol/L (200 mg/dL), fluid should be changed to 5% dextrose with 0.45% NaCl at 150–250 mL/h	
	In hypernatraemic or eunatraemic patients: 0.45% NaCl at 250–500 mL/h and when blood glucose reaches 11 mmol/L (200 mg/dL), it should be changed to 5% dextrose with 0.45% NaCl at 150–250 mL/h	
	Continue FRIII	
	In young children with mild to moderate DKA 0.05 units/ kg/h is sufficient to control and in severe DKA and in adolescent patients 0.1 units/kg/h should start **after 1 h of fluid replacement therapy**	
	In children with HHS insulin need is less. So a dose of 0.025 to 0.05 units/kg/h should start **after 1 h of fluid replacement**	

(continued)

Table 12 (continued)

Intervention	DKA, EDKA and HHS 0–60 min: Resuscitate, diagnose and treatment	Monitoring, ongoing lab work-up
	Continue basal insulin if taking before K replacement if needed	
	If infection is suspected by and evidenced by CXR, DC >25,000, neutrophil >80% then a broad spectrum injectable antibiotic have to start. Culture report takes time so need not wait for that	
Bicarbonate therapy	At pH >7.0 insulin therapy blocks lipolysis and resolves ketoacidosis without use of HCO3. Use of HCO3 in these cases may cause hypokalemia, decreased tissue oxygen uptake and risk of cerebral oedema	
	Arterial pH 6.9–7.0 = 50 mmol NaHCO3 in 200 mL sterile water with 10 mEq KCl may be administered over an hour till pH >7.0	
	Arterial pH < 6.9 = 100 mL of NaHCO3 in 400 mL sterile water with 20 mEq KCL at the rate of 200 mL/h for 2 h until pH >7.0	
Phosphate, magnesium and calcium therapy	Very rarely used though there are some nominal deficits. But in symptomatic cases these are supplemented	
	Significant malnutrition is associated with such deficits	
	6–24 HR: Improvement & resolution monitoring	
Fluid Replacement Continues, FRIII Continues, K replacement if needed	0.9% NaCl 1 l over 4 h, then	**WORK-UP**: **6 HOURLY** and then **12 HOURLY** serum K, HCO3, venous blood gas for pH **HOURLY:** Capillary blood glucose, ketones, cardiac monitoring, BP, pulse, respirations, pulse oximetry, fluid input/output chart, neurological observations
	0.9% NaCl 1 l over 6 h, then	
	0.9% NaCl 1 l over 6 h.	
	Continue FRIII	
	K replacement if needed	
	Once blood glucose falls near 13.9 mmol/L (250 mg/dL), then insulin infusion should be reduced to 0.02–0.05 units/kg/h and a 5% dextrose in saline have to add while maintaining blood glucose 11–17 mmol/L (200–300 mg/dL)	
	Resolution criteria FOR DKA, EDKA and HHS	
	Criteria for resolution in DKA, EDKA (except glucose)	
	1. Plasma glucose <11 mmol/L (< 200 mg/dL)	
	2. Serum HCO3 is >18 mEq/ L	
	3. Blood ketones <0.6 mmol/L	
	4. Venous pH is >7.3, and	
	5. Anion gap is <10	
	Criteria for resolution of HHS:	
	1. Plasma glucose <14–16.7 mmol/L (250–300 mg/dL)	
	2. Plasma osmolality <315 mOsm/kg	

(continued)

Table 12 (continued)

Intervention	DKA, EDKA and HHS 0–60 min: Resuscitate, diagnose and treatment	Monitoring, ongoing lab work-up
	3. Improvement in haemodynamic and mental status	
	Resolution pitfalls: Urinary ketone clearance takes time even after resolution. As BOHB from blood converts to form AcAc after resolution which is abundant in urine	
	HCO3 alone cannot be relied as resolution of DKA. It is due to high amount of 0.9% NaCl saline infusion causes hypercholeraemic acidosis which lowers HCO3	
	24–48 Hours: resolution & discontinuation of FRIII	
FRIII to VRIII	If DKA/ HHS is resolved: Ketones <0.6 mmol/L but NOT eating & drinking then switch from FRIII to **VRIII** (Variable Rate Intravenous Insulin Infusion)	
	VRIII is based on standard rate such as glucose <4 mmol/L = 0 units/kg/h, 4.1–8 mmol/L = 1 units/kg/h, 8.1–12 mmol/L = 2 units/kg/h and so on	
VRIII to S.C. Insulin	VRIII can be discontinued at mealtime. If earlier taking subcutaneous insulin the same insulin can restart with the diabetes team advice of titration	
	VRIII have to continue 30–60 min after first subcutaneous insulin injection	
For newly diagnosed T1D and T2D: Insulin therapy	Total last 24 h insulin should be added and 30% reduction is done. This value have to divide by 5 and 1/5th is given with each meal as rapid acting insulin and 2/5th can be given as basal analogue insulin which is called BASAL BOLUS REGIMEN	
	The 30% reduced amount from last 24 h total insulin use can be used as TWICE DAILY REGIMEN. The amount have to divide by 3 and 2/3 have to take with breakfast and 1/3 with evening meal within the interval of 12 h	
VRIII TO CSII	To reconnect the insulin pump, normal basal rate have to start and a mealtime bolus have to be given. VRII then have to stop 1 h later	

9.2 Management: Acute Hyperglycaemic Crisis Due to COVID-19

The pandemic COVID-19 infection increases the risk of precipitating atypical DKA, HHS or mixed crisis and stress hyperglycaemia with ketones. The recent guideline from ABCD (Association of British Clinical Diabetologists) named 'COVID: Diabetes' (**CO**ncise ad**V**ice on **I**npatient **D**iabetes) has outlined to manage COVID-19 in hyperglycaemic crisis in diabetes (ABCD

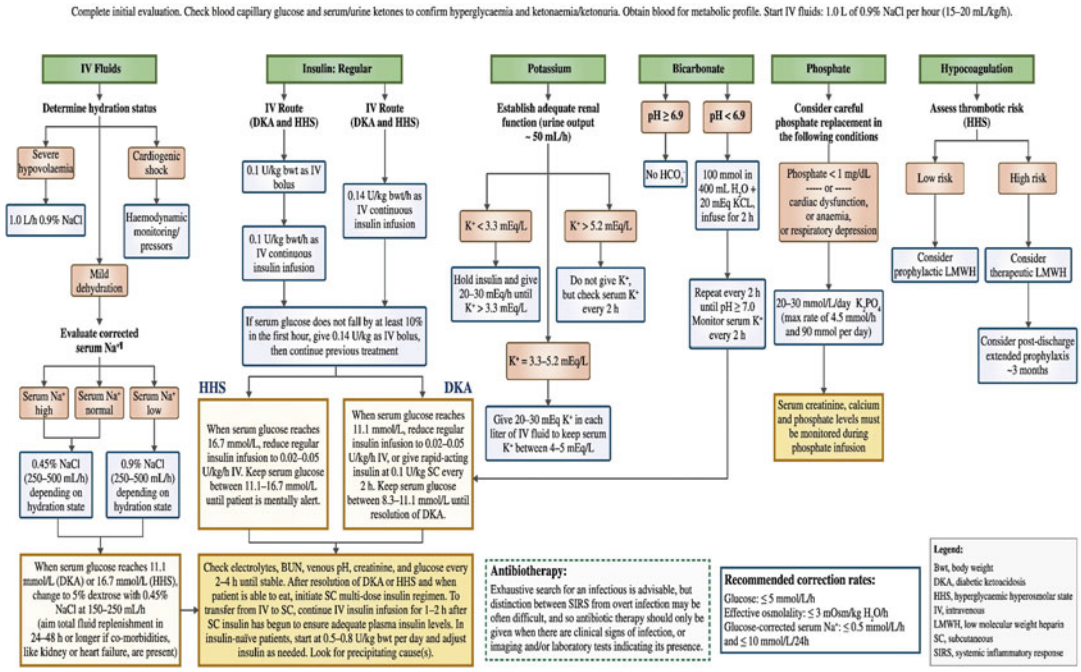

Fig. 6 DKA and HHA management algorithm reproduced with permission (Cardoso et al. 2017)

2020). This guideline is based on UK experience of COVID-19 management and will be updated further when more evidences will be available. COVID-19 infection in known or unknown people with diabetes increases the risk of acute hyperglycaemia with ketones, DKA and HHS. Poorly controlled elderly diabetes patients are more susceptible to COVID-19 and its complications. Because hyperglycaemia can subdue immunity by disrupting the normal function of WBC and other immune cells. Good glycaemic control and following sick day rules are key to reduce risk apart from taking personal protection and social distancing.

Table 13 shows COVID-19 specific management of acute hyperglycaemic crisis paraphrased from the 'COVID: Diabetes' guideline (ABCD 2020).

9.3 Management: Some Controversial Issues

- **0.9% NaCl vs Hartmann's solution**: In a recent RCT (Yung et al. 2017), comparing Hartmann's solution with 0.9% NaCl in 77 children with DKA, it was observed that slightly quicker resolution of acidosis can be achieved with Hartmann's solution in severe DKA. There was however, no difference regarding time required to shift from intravenous to subcutaneous insulin.
- **0.9%NaCl vs Ringer Lactate solution**: A RCT showed no benefit from using Ringer Lactate solution compared with 0.9% NaCl in terms of pH normalization. But Ringer Lactate solution made longer time to reach blood glucose level of 14 mmol/L because lactate converts into glucose (Van Zyl et al. 2011).
- **0.9%NaCl vs Plsma-Lyte 148**: The concern regarding excessive administration of normal saline in DKA is hyperchloremia which can lead to non-anion gap metabolic acidosis. Although self-limiting in nature, this hyperchloremic metabolic acidosis is now believed to have a harmful impact on multiple organs of body like kidneys, myocardium etc. (Eisenhut 2006; Kraut and Kurtz 2014). Plasma-Lyte 148 when compared to normal saline has shown to decrease occurrence of

Table 13 COVID-19 and acute hyperglycaemic crisis in diabetes (ABCD 2020)

Changes seen	Key difference with COVID-19	Action suggested
Risk of early admission	T2D and those on SGLT2i are greater risk	On admission blood glucose checking for everyone
	COVID-19 precipitates DKA or HHS or atypical mixed type	Ketones for all diabetes admission
		Ketones for everybody with admission glucose >12 mmol/L
	Risk of hyperglycaemia with moderate ketones due to stress hyperglycaemia	SGLT2i and Metformin tablets should be immediately stopped on admission
		Safety of ACEi, ARB and NSAID should be reviewed
		10–20% glucose should be used where ketosis persists even usual protocol of DKA is used
Severely sick on admission	Fluid infusion rate may differ in DKA/ HHS and there is evidence of 'lung leak' or myocarditis	After correcting dehydration, rate of fluid infusion should be adjusted in lung leak or myocarditis cases
		Early diabetes specialist team and critical care team involvement needed
Inpatient area	Due to huge demand infusion pumps may not be enough as huge need in ICU	Subcutaneous insulin have to start with basal insulin support to manage hyperglycaemia, DKA or HHS or mixed cases
ICU	Insulin resistance is significantly increased in T2D admitted in ICU	Insulin infusion protocols need amendment. It is seen patients need 20 units/h even
	Higher doses of insulin is required	Patients sometime nursed prone so feeding may be interrupted accidentally with risk of hypoglycaemia

hyperchloremia (Andrew and Patrick 2018; Chua et al. 2012). A systematic review by Gershkovich et al. (Gershkovich et al. 2019) might help aid the decision regarding fluid choice in future.

- **0.9% NaCl vs Ringer Acetate solution:** Though Ringer Acetate is not a popular choice but it has almost similar composition like Ringer Lactate. But its use in hepato-renal emergencies are established (Ergin et al. 2016). Figure 7 shows water shift in hyperglycaemic emergencies with different infusion fluids. The figure is reproduced with permission (Cardoso et al. 2017).
- **Infusion rate**: Regarding infusion rate, rapid administration is feared to increase likelihood of cerebral edema especially in children and young adults. The JBDS guidelines therefore recommend gradual correction of fluid deficit over 48 h unless clear signs of hypovolemic shock are present (Dhatariya 2014).
- **Arterial or venous sample**: the difference between venous and arterial pH is 0.02–0.15 and the difference between arterial and venous HCO3 is 1.88 mmol/L. These neither affect the diagnosis nor the treatment. But getting arterial sample is risky and painful. So venous sample is widely accepted.
- The target with fluid administration in HHS is to achieve an hourly drop of 3–8 mOsm/kg in osmolality and 5 mmol/L in glucose. Some adjustments in fluid administration rate and solution type are required if these targets are not being met (Scott et al. 2015). These scenarios are mentioned in Table 14 (Scott et al. 2015).

9.4 Management: DKA and EDKA IN Pregnancy

DKA is an emergency during pregnancy and may cause fetal loss which is around 10–25%. The incidence rate is 1–3%. The main causes and precipitating factors are (Savage et al. 2011):

- Starvation: accelerated maternal response ends up in DKA in women with diabetes
- Increased flux of glucose from mother to fetus and placenta: due to increased transporter GLUT-1.

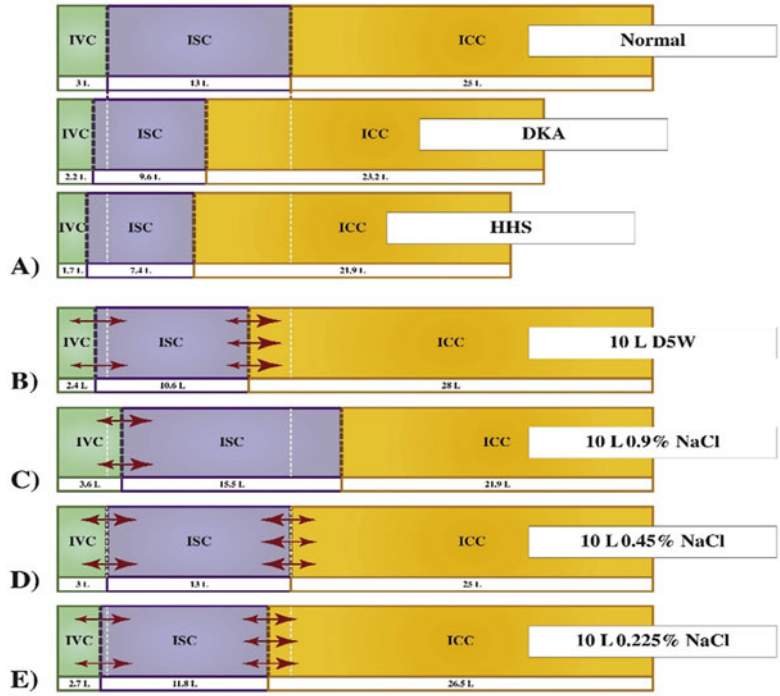

Fig. 7 *ICC* Intracellular compartment, *ISC* Interstitial compartment, *IVC* Intravascular compartment. **Panel A**: Total body water distribution in normal state; **Panel B**: After correction of water deficit with 5% Dextrose water shows suboptimal replenishment of IVC, ISC and excessive rehydration of ICC; **Panel C**: Correction with 0.9% NaCl made exclusive distribution in extracellular compartment resulting excessive hydration of IVC and ISC; **Panel D**: Correction with 0.45% NaCl shows replenishment similar to fluid lost from IVC, ISC and ICC. It is probably the best option; **Panel E**: Correction with 0.225% resulted in suboptimal replenishment of IVC, ISC but excessive hydration of ICC

Table 14 Scenarios with serum osmolality and fluid infusion

Scenario	Solution
Plasma osmolality declining at appropriate rate but plasma sodium increasing[a]	Continue 0.9% normal saline
Plasma osmolality declining inappropriately (<3 mOsm/kg/h) or increasing with inadequate fluid balance	Increase rate of 0.9% normal saline
Plasma osmolality increasing with adequate fluid balance	Switch to 0.45% normal saline
Osmolality falling at rate > 8 mOSm/kg/h	Decrease rate of 0.9% normal saline

[a]With fall in serum glucose level, rise in serum sodium level is expected due to shift of water in intracellular space. Drop of blood glucose by 5.5 mmol/L = rise of Na by 2.4 mmol/L (Scott et al. 2015)

- Higher progesterone level: induces respiratory alkalosis which results in metabolic acidosis that reduces buffering capacity.
- Precipitating factors: UTI, hyperemesis gravidarum, new onset T1D, KPD, insulin omission, insulin pump malfunction, glucocorticoid use for inducing fetal lung maturity, use of terbutaline to prevent premature labour.
- DKA and EDKA management is same like non-pregnant cases.

Table 15 Key calculations

Anion gap	Anion gap = Na – (Cl + HCO3); normal is12 ± 2 mmol/L
	In DKA anion gap is 20–30 mmol/ L.
	An anion gap >35 mmol/L suggests concomitant lactic acidosis
Corrected sodium	Corrected Na = measured Na +2 (Glucose-5.6)/5.6
	Corrected Na is needed to estimate fluid replacement in DKA/HHS when dehydration is mild to moderate
	Web based calculation: https://www.mdcalc.com/sodium-correction-hyperglycemia
Effective osmolality	Serum osmolality = 2Na + glucose + urea
Fluid calculation in children	REQUIREMENT = DEFICIT + MAINTENANCE
	Holliday – Segar formula:
	100 mL/kg/day for first 10 kg
	50 mL/ kg/day for next 10 to 20 kg
	20 mL /kg/day for each kg above 20 kg
	Hourly rate = ({deficit – Initial bolus} /48 h) + maintenance/h

9.5 Management: Key Calculations

Table 15 shows the key calculations needed during management of acute hyperglycaemic crisis (Wolfsdorf et al. 2018).

10 Complications

The probable complications of DKA and HHS are tabulated in Table 16 (Savage et al. 2011; Scott et al. 2015; Khazai and Umpierrez 2020).

Cerebral Edema

Cerebral edema (CE)' is rare and most feared iatrogenic complication of DKA in younger children and in newly diagnosed T1D. It is associated with high mortality and neurodisability & neurocognitive difficulties in survived cohorts. Headache, lethargy, papillary changes and seizure are key manifestation.

Risk of CE found in a study with higher plasma urea, lower arterial pCO_2 and $NaHCO_3$ therapy in DKA (Glaser et al. 2001). Interleukin-1 and 6 (IL-1 and IL-6) are the cytokines that initiate the inflammatory response accompanied by DKA. It is postulated that this IL-1 is linked with the pathogenesis of CE. NLRP3 (nucleotide-binding domain and leucine-rich repeat pyrin 3 domain) is an inflammasome which generates active form of IL-1 in response to hyperglycaemia acts as osmosensors to cause CE in DKA. It contributes to CE and infarction by making tight junctions leaky (Eisenhut 2018). Some studies have found that initial bolus of rehydration fluid and bolus insulin might have a role (Carlotti 2003).

Table 17 shows the diagnosis of cerebral edema in DKA (Wolfsdorf et al. 2018).

The management of cerebral edema is difficult and involves careful administration of fluids with strict blood pressure control and infusion of mannitol or hypertonic saline. Mannitol is administered at dose of 0.5–1 g/kg body weight. The calculated dose is administered over a period of 10–15 min and if necessary repeated after 30 min (Wolfsdorf et al. 2018). If mannitol is not available or if there is no response to mannitol, 3% hypertonic saline can be given at calculated dose of 2.5–5 ml/kg. The time for administration is again 10–15 min (Wolfsdorf et al. 2018).

Regarding mannitol versus hypertonic saline selection, controversies exist but recent data suggests lower mortality rate with mannitol (Wolfsdorf et al. 2018).

Figure 8 Pathogenesis of cerebral edema in DKA. The figure is reproduced with permission (Carlotti 2003).

Table 16 Complications of DKA, EDKA AND HHS

Complications	Cause and remedy	Risk probability
Hypoglycaemia	High dose insulin can cause	In HHS risk probability is more than DKA as insulin sensitivity is more in HHS
	Management protocol should follow throughout and frequent monitoring is needed. 5–10% dextrose saline is needed with FRIII when sugar came down	
	The episode happens for short duration only	
Hypokalemia	Use of excessive high dose of insulin and use of HCO3 can cause it	Risk is high in both DKA and HHS
	Potassium level should be monitored frequently and replacement should be done if inadequate	
Pulmonary or arterial or venous thromboembolism	DKA and HHS patients are at risk of thromboembolism especially in case of central venous catheter use in shock patients	Risk is medium to low. Messenteric vessel thrombosis in extreme rare cases may be found
	Prophylactic LMWH should be given in high risk patients based on clinical evaluation	
Nonanion gap hyperchloremic acidosis	It occurs due to loss of ketoanions through urine which are needed for HCO3 formation	The risk is low
	Moreover, due to high amount of 0.9% NaCl saline infusion, increased amount of chloride reabsorption occurs. Hyperchloremic acidosis resolves during management	
	In DKA in pregnancy this is seen sometime	
Cerebral edema, central pontine myelinolysis	Cerebral edema (CE) incidence is 0.7–10% of children under 5 years of age. It is rare in adults with DKA and in HHS	Avoidance of aggressive hydration and maintaining blood glucose <11 mmol/L can prevent
	Headache, lethargy, papillary changes and seizure are key manifestation	Risk of CE is low if following guidelines properly
	Mortality rate of CE is high and it is around 57–87% of all deaths of DKA (Kitabchi et al. 2009)	
ARDS, DIC	Iatrogenic reduction in colloid osmotic pressure may lead to accumulation of water in lungs, decrease lung compliance and hypoxemia	Risks are very low
	Monitoring blood oxygen saturation, lowering fluid intake and adding colloid fluid can correct ARDS	
	DIC is a rare complication of HHS	
Stroke, AMI	Stroke and MI are rare complication in HHS. Predisposing factors are volume depletion with increased viscosity, increased levels of PAI-1, hyperfibrinogenaemia etc.	Risk is low in cases where the guideline for fluid repletion is followed properly
	Early adequate hydration is helpful	
Coma	Rarely associated in HHS with serum osmolality <330–340 mOsm/kg and in hypernatraemic than hyperglycaemic	Risk is very low
	ICU management is needed	
Foot ulceration	Rarely occurs in DKA in children and young adults buy in elderly could happen in obtunded or uncooperative cases. The heels should be protected and daily foot checks should be done	High risk in elderly cases of HHS
	In HHS patients who are usually elderly with comorbidities it is a high risk especially in those who are obtunded or need to long stay to recover. The heels should be protected and daily foot checks should be done	

Table 17 Diagnosis of cerebral EDEMA

A. Diagnostic criteria
Abnormal verbal or motor response to pain
Decorticate or decerebrate posture
Cranial nerve palsy
Abnormal neurogenic breathing pattern (like grunting, tachypnea, Cheyne-Stoke respiration, apneusis)
B. Major criteria
Altered/fluctuating state of consciousness
Sustained decreasing heart rate (>20 beats per minute) not attributable to any other reason
Age-inappropriate incontinence
C. Minor criteria
Vomiting
Headache
Lethargy
DBP >90 mmHg
Age < 5 years
If one diagnostic criterion or 2 major criteria or 1 major and 2 minor criteria are present, then diagnostic sensitivity for cerebral edema is 92% with false positive rate of only 4%. However signs that occur before start of treatment should not be included

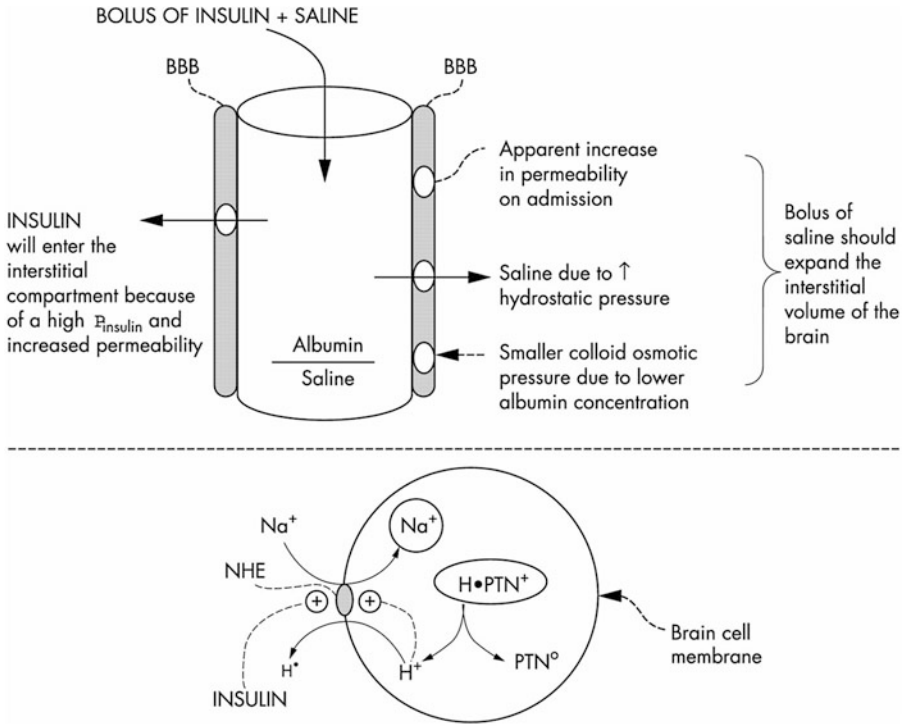

Fig. 8 A bolus of saline could expand the intracranial interstitial volume. A bolus of insulin could expand the intracerebral ICF volume (Scott et al. 2015)

11 Prevention

Management of acute hyperglycemic emergencies is not complete until steps are taken to prevent recurrence of future episodes. Diabetes education is an important component of prevention strategy. The education should be tailored to the individual's requirement. This is only possible after trigger has been identified. Ideally this should be delivered by a specialized diabetes educator (Karslioglu French et al. 2019).

Proper education regarding sick day rules is essential to prevent recurrence. The important components of sick day management include education regarding hydration, glucose and ketones monitoring, continuation of basal insulin and timely contact with health care provider (Karslioglu French et al. 2019). Since the process of ketogenesis occurs in the absence or deficiency of insulin, its recurrence can be avoided. One of the major reasons for recurrence of DKA is non-compliance with insulin in teenagers of less privileged areas who are being most commonly affected. These patients can benefit from targeted community support programs (Dabelea et al. 2014).

Patient on insulin pump is at high risk of DKA in case of pump failure. Therefore one should be educated regarding its care. One should also have an emergency contact number for technical support. In case of pump failure, one might require multiple daily injections to prevent DKA as insulin reserve in body is very limited for a patient on insulin pump. Therefore one must be educated in this regard and advised to carry a reserve of long-acting insulin (Jesudoss and Murray 2016; Rodgers 2008).

12 Conclusion

DKA, EDKA and HHS are avoidable metabolic emergencies both of which can be decreased in incidences with education regarding diabetes management in sick days. The management principles are different for each condition but generally require hospitalization and intravenous fluids with electrolytes. While close monitoring during episode has decreased mortality rate, there are still some controversial areas like fluid choice for rehydration. Due to availability of updated guidelines management is much better now. The structured diabetes education and abiding by sick day rules made significant improvement in reducing the recurrences of acute metabolic crisis of diabetes.

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