DIABETIC KETOACIDOSIS: EVALUATION OF THERAPEUTIC OUTCOMES, AND KNOWLEDGE, ATTITUDE AND PRACTICES OF PHYSICIANS AND PHARMACISTS IN HOSPITAL PULAU PINANG

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by

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This being the reason

I dedicate it to them,

for whom I was not there

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Foremost, I crave to thank Allah Almighty, for I was kept blessed and protected throughout my study, and bestowed when sent to people who I am greatly indebt of.

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ABG	Arterial blood gas
BBB	Blood brain barrier
BGL	blood glucose level
bpm	beats per minute
CII	Continuous insulin infusion
CO_2	Carbon dioxide
CPT-I	Carnitine palmitoyltransferase-I
CPT-II	Carnitine palmitoyltransferase-II
CSF	Cerebrospinal fluid
CV	Cardiovascular
DFU	Diabetic foot ulcer
DKA	Diabetic ketoacidosis
dL	Deciliter
DM	Diabetes mellitus
dys	Days
EBP	Evidence based practice
ECG	Electrocardiography
ED	Emergency department
FFA	Free fatty acid
g	Gram
GP	General Practitioner
h	Hour
H^+	Hydrogen

H_2O	Water
HCO_3^-	Bicarbonate
HHS	Hyperglycemic hyperosmolar state
HOD	Head of department
HPP	Hospital Pulau Pinang
HSL	Hormone sensitive lipase
ICD	International classification of diseases
ICP	Integrated care pathway
ICRH	Insulin counterregulatory hormones
IDDM	Insulin dependent diabetes mellitus
IM	Intramuscular
IU	International unit
IV	Intravenous
K^+	Potassium
KCl	Potassium chloride
kg	Kilogram
KPO_4	Potassium phosphate
L	Liter
LADA	Latent autoimmune diabetes
mEq	Milliequivalent
MFUC	Medical follow up clinic
mg	Milligram
MI	Myocardial infarction
MIDD	Maternally inherited diabetes and deafness

mL	milliliter
mmol	millimole
MODY	Maturity onset of diabetes of the young
MOH	Ministry of health
mOsm	milliosmole
n	number
Na^+	Sodium
NADH	Nicotinamide adenine dinucleotide
$NaHCO_3$	Sodium bicarbonate
NDDM	Newly diagnosed diabetes mellitus
NIDDM	Non-insulin dependent diabetes mellitus
NS	Normal Saline
O_2	Oxygen
OAD	Oral antidiabetic
ºC	Centigrade
pH	Power of hydrogen
PO_4	Phosphate
RL	Ringer Lactate
SC	Subcutaneous
SOP	Standard operating procedure
SPSS	Statistical Package for the Social Sciences
SSI	Sliding scale insulin
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

TB	Tuberculosis
TBW	Total body water
TCA	Tricarboxylic acid
TSL	Tissue sensitive lipase
vs.	Versus
μL	Microliter

DIABETIK KETOASIDOSIS: PENILAIAN DAPATAN TERAPEUTIK DAN PENGETAHUAN, SIKAP DAN PRAKTIS PAKAR PERUBATAN DAN AHLI FARMASI DI HOSPITAL PULAU PINANG

ABSTRAK

Kelaziman Diabetes Mellitus (DM) dan ko-morbiditi yang berkaitan dengannya adalah tinggi. Walaubagaimanapun tidak terdapat protokol pengawalan untuk Diabetic Ketoacidosis (DKA) setakat ini. Data mengenai keadaan ini juga tidak begitu sempurna. Tujuan kajian ini ialah untuk merekodkan kadar kelaziman DKA dan dapatan rawatannya. Ianya juga bertujuan meninjau pengetahuan, sikap dan praktis dalam kalangan professional kesihatan yang terlibat secara langsung dalam rawatan DM dan DKA. Untuk bahagian pertama, kajian secara restrospektif telah dijalankan di Hospital Pulau Pinang. Profil pesakit DKA di pilih secara teknik persampelan universal berdasarkan kriteria yang telah ditetapkan dan analisanya dijalankan dengan menggunakan Statistical Package for Social Sciences (SPSS) version 16. Purata umur pesakit adalah 47.7 ± 16.3 tahun dimana kebanyakannya adalah dalam kalangan orang melayu (47%). DKA didapati lebih lazim dalam kalangan T2DM (51.5%), yang mengalami hipertensi (54.5%) dan pesakit dislipidemik (43.0%). Kebanyakkan pesakit mengalami loya dan muntah (61.4%) dan seringkali diiringi oleh sepsis (31.9%). Doktor yang merawat juga mendapati 83.3% pesakit mengalami dehidrasi. Laporan makmal menunjukkan paras glukos dalam darah ialah 30.4 ± 13.3 mmol · L^{-1}, arterial *p*H 7.15 ± 0.16, arterial bicarbonate pada 9.7 ± 5.5 mmol · L^{-1} dan ketones pada 4.6 ± 1.7 mmol · L^{-1}. Adalah juga di dapati yang pesakit baru diabetes (NDDM), pesakit yang meninggal dunia dan dimasukkan ke ICU mempunyai keadaan DKA yang lebih serius. Didapati

rawatan awal DKA di unit rawatan kecemasan (ED) adalah tidak lengkap dan tidak sejajar dengan garispanduan antarabangsa. Perkara yang sama di perhatikan untuk rawatan dalam wad. Juga didapati profil biokimia yang berkaitan dengan DKA adalah tidak berada dalam julat yang dibenarkan ketika pesakit keluar dari hospital. Selain dari 17.6% pesakit yang meninggal dunia juga didapati 13.7% pesakit tidak mempunyai matlamat rawatan yang sempurna. Bahagian kedua kajian ini dijalankan secara prospektif. Soal selidik telah diedarkan dalam kalangan ahli farmasi klinikal dan pakar perubatan di Unit Rawatan Rapi (ICU), Medical Follow Up Clinic (MFUC), and ED. Kadar tindak balas keseluruhan soal selidik adalah 64.3% dengan sambutan yang paling kurang dari ICU. Pengetahuan purata dan amalan responden didapati mencukupi. Doktor ICU menunjukkan skor maksimum pengetahuan (6.4 ± 1.4) manakala nephrologists menjaringkan maksimum dalam soalan berasaskan amalan (7.4 ± 0.9). Nephrologists juga menunjukkan sikap yang lebih baik (39.1 ± 3.7) di antara kepakaran manakala secara kolektif, sikap seluruh peserta juga didapati positif ke arah pendekatan berpusatkan pesakit. Amalan ahli farmasi dan doktor adalah selari antara satu sama lain yang walaupun ketara, tetapi masih suboptimal apabila dibandingkan dengan garis panduan antarabangsa. Adalah didapati bahawa kadar kelaziman dan kematian DKA di kalangan penduduk pelbagai etnik Malaysia adalah lebih tinggi daripada kadar yang dilaporkan antarabangsa dan serantau. Walaupun amalan doktor dan ahli farmasi adalah sederhana, ini bagaimanapun perlu banyak pembaikan yang mudah boleh diatasi dengan membangun atau mengguna pakai protokol.

DIABETIC KETOACIDOSIS: EVALUATION OF THERAPEUTIC OUTCOMES AND KNOWLEDGE, ATTITUDE AND PRACTICES OF PHYSICIANS AND PHARMACISTS IN HOSPITAL PULAU PINANG

ABSTRACT

Incidence of Diabetes Mellitus (DM) and its associated acute co-morbidities is increasing. However, there is no Diabetic Ketoacidosis (DKA) treatment protocol in Malaysia at this point. There is no baseline data available for DKA in Malaysia as well. This study aims to record incidence rate of DKA and its treatment outcomes in Malaysian population. It is also intended to get an insight of knowledge, attitude and practices of healthcare professionals that are directly involved in management of DM and DKA. For first part, the study was done retrospectively at Hospital Pulau Pinang (HPP). DKA patient profiles were recorded by using universal sampling technique based on inclusion criteria and further analyzed using Statistical Package for Social Sciences (SPSS)® version 16. Of total 132 DKA patients, mean age of patients was 47.7 ± 16.3 years while most admissions were attributed to Malay patients (47%). DKA was more prevalent in T2DM (51.5%) patients followed by hypertension (54.5%) and dyslipidemia (43.0%). Most patients (61.4%) registered complaint of nausea and vomiting, and were accompanied with sepsis (31.9%) whereas attending physicians observed 83.3% patients to be dehydrated. Moreover, with mean blood glucose level at 30.4 ± 13.3 mmol · L^{-1}, arterial *p*H at 7.15 ± 0.16, arterial bicarbonate at 9.7 ± 5.5 mmol · L^{-1} and ketones at 4.6 ± 1.7 mmol · L^{-1}, chief DKA biochemical profiles rendered patients to be experiencing moderate episode of DKA, on average. It was also observed that newly diagnosed diabetes mellitus (NDDM) patients, deceased patients and ICU referred patients had more severe event of DKA than the rest of patients. It was found

that initial management of DKA patients in emergency department (ED) and in-patient management were not completely at par with international guidelines. Furthermore, biochemical profiles related to DKA were not within recommended limits at the time of discharge. Apart from 17.6% deceased patients, 13.7% were found to be not at recommended treatment goal. Second part of study was conducted prospectively. Questionnaires were distributed among clinical pharmacists and physicians of Intensive Care Unit (ICU), Medical Follow Up Clinic (MFUC), and ED. With total 92 included questionnaires, overall response rate of questionnaire was 64.3% with least response from ICU. Average knowledge and practices of respondents were found adequate. ICU physicians showed maximum score of knowledge (6.4 ± 1.4) whereas nephrologists scored maximum in practice based questions (7.4 ± 0.9). Nephrologists also showed better attitude (39.1 ± 3.7) across specialties while collectively, attitude of rest of the participants was also found positive toward patient centric approach. Pharmacists and physicians practices were parallel with each other which were although appreciable; these were still suboptimal when compared with international guidelines, however. The incidence and mortality rates of DKA in multiethnic population of Malaysia are higher than international and regional reported rates. Moreover, though the practices of physicians and pharmacists are sound on average, these need plenty of improvement which could easily be overcome by developing or adopting a protocol, however.

CHAPTER 1

INTRODUCTION

1.1 Diabetes Mellitus

Diabetes Mellitus (DM) is a life long, chronic and to-date, an incurable disorder of metabolic continuum that could be best defined as persistent hyperglycemia. It is among the 10 most prevalent diseases of the world according to World Health Organization and directly contributes in mortality rates of cardiovascular and tuberculosis related deaths (World Health Organization., 2009). Prevalence of diabetes is increasing globally and is estimated to affect 439 million people by the year 2030. The increase in number of adults with diabetes is expected to be 20% and 69% for developed and developing countries, respectively, when comparing with prevalence of DM in 2010 (Shaw *et al.*, 2010; IDF, 2012). This reciprocates that DM and complications attributed to DM will increase and so will their cost of management (Umpierrez and Kitabchi, 2003; Kitabchi *et al.*, 2006; Mathers *et al.*, 2008).

1.1.1 Types of Diabetes Mellitus and its complications

Diabetes is categorized in two main types namely type 1 and type 2 diabetes. In case of destruction of beta cells present in islet cells of Langerhans, there is an absolute deficiency of insulin production. This condition is type 1 diabetes mellitus (T1DM), usually occurs in childhood and requires lifelong administration of insulin as a part of management. Patients of type 2 diabetes mellitus (T2DM) have a relative deficiency of natural insulin which is not sufficient to carry out the normal physiological functions. Moreover, insulin resistance is another hindrance for insulin to carry on its appropriate physiological function even when it is secreted normally. Hence, T2DM is managed by

the drugs facilitating production of natural insulin from islet cells, and which tend to reduce the insulin resistance. Though uncommon, apart from these two main types, DM also includes maturity onset of diabetes in the young (MODY), latent autoimmune diabetes in adult (LADA), maternally inherited diabetes with deafness (MIDD) and gestational diabetes (Alberti *et al.*, 1998; Holt *et al.*, 2010).

Based on the time for a complication to develop, DM is accounted for number of chronic and acute complications. Chronic complications comparatively take long time to develop and are further divided in microvascular and macrovascular complications. Patients with lower degree hyperglycemia are susceptible to develop microvascular complications. These disorders are associated with severity and duration for hyperglycemia and include retinopathy, nephropathy, neuropathy, diabetic foot and erectile dysfunction (Stephenson and Fuller, 1994). Contrarily, hyperglycemia does not have such strong association with macrovascular complications i.e. cerebrovascular and cardiovascular disorders (Holt *et al.*, 2010). These complications are associated with insulin resistance and might have been brewing since pre-diabetes phase of a patient. Actual risk factors for these disorders are hypertension, obesity and dyslipidemia. Therefore, even with fairly controlled glycemic level, patients of DM are at risk of an eventful life which may lead to mortality (Danaei *et al.*, 2006; Holt *et al.*, 2010). Apart from chronic complications, for which DM control is a mild risk factor, acute complications are directly influenced by glycemic control since fluctuation in blood glucose level may cause either hyper- or hypo- glycemia (Stephenson and Fuller, 1994; Pickup and Williams, 2003; Holt *et al.*, 2010).

There are two states of acute DM complications i.e. hypoglycemia and hyperglycemia. Hypoglycemia, also known as dead-in-bed syndrome, occurs in patients while they adjust themselves with their diabetes management plan (Tu *et al.*, 2008). Mortality rate due to hypoglycemia varies and fatality is usually considered as a result of cardiovascular abnormalities induced by hypokalemia and activation of sympathoadrenal system (Frier *et al.*, 2011). Hypokalemia and cardiovascular abnormalities are also observed in hyperglycemia provoked acute complications of DM. Acute hyperglycemic conditions include Hyperglycemic Hyperosmolar State (HHS) and Diabetic Ketoacidosis (DKA) (NIH, 1995). There is a small difference between these states and these complications could be overlapped by Alcoholic Ketoacidosis, Lactic Acidosis and Hyperchloremic Acidosis (Lebovitz, 1995; Chiasson *et al.*, 2003). HHS is a resultant state of relative insulin deficiency whereas DKA is experienced in case of absolute insulin deficiency or profound insulin resistance. HHS and DKA differ in terms of glucose concentration, presence of ketone bodies and serum osmolarity (Kitabchi *et al.*, 2006). Alcoholic ketoacidosis is seen if patient keeps consuming alcohol without intake of food. Hyperchloremic acidosis is caused due to loss of bicarbonate ion (HCO_3^-) by either gastrointestinal tract abnormality or renal failure. Lactic acidosis, observed as a result of DKA, is actually an outcome of hypoxia. Abovementioned complications are classified under metabolic acidosis (Dugdale, 2011).

1.1.2 Diabetic Ketoacidosis

DKA is an acute complication of DM. Its main attributes are hyperglycemia induced ketosis which in turn, causes acidosis. Hyperglycemia may vary from 3.5 mmol $\cdot$ L^{-1} to 55 mmol $\cdot$ L^{-1} in DKA (Graham, 2008). Ketones, even found in a trace, are firm proof of

DKA provided that arterial blood gas (ABG) *p*H is ≤ 7.30 and bicarbonate is ≤ 19 mmol · L^{-1} (NICE, 2004; Kitabchi *et al.*, 2006; Savage *et al.*, 2011). These factors vary from patient to patient and hence, there is no absolute definition of DKA (Lebovitz, 1995).

1.2 Statistics of Diabetic Ketoacidosis

1.2.1 Incidence rate of Diabetic Ketoacidosis

DKA was first documented in 1828 and subsequently, in 1854 (John, 1935). A detailed account of DKA was given in 1886 which cited the work of various researchers (Dreschfeld, 1886). Strikingly, all the discussed cases shared a common endpoint i.e. death; as there was no cure for diabetic patients until the discovery of insulin. Moreover, any rate of incidence or mortality for DKA was neither recorded nor mentioned in it.

The ultimate endpoint for DKA was death before the discovery of insulin and such disappointment seems to be the reason of unavailability of any medical notes. First study to report the number of DKA cases was available after the discovery of insulin in which 276 cases were studied over a period of 10 years. Six reports were published at different occasions that discussed characteristics of DKA and its treatment (Baker, 1936). Considering the aforementioned figure, the number of cases after the discovery of insulin was 27.8 per year. For last three decades, the incidence rate of DKA in well managed facilities was calculated to be around 4.6 to 13.4 patients of DKA per 1000 diabetic admissions ((Johnson *et al.*, 1980; Faich *et al.*, 1983; Wright *et al.*, 1990; Stephenson and Fuller, 1994; Umpierrez and Kitabchi, 2003). Currently, incidence rate in developed countries is recorded to be approximately 8 patients of DKA per 1000 diabetic admissions (Henriksen *et al.*, 2007; Weinert *et al.*, 2012). However, situation in

developing countries tends to be higher and up to sevenfold increase in incidence of DKA was observed in Korea over period of 20 years (Ko *et al.*, 2005).

1.2.2 Mortality rate of Diabetic Ketoacidosis

Number of deaths was an endpoint of nearly 90% of all diabetic coma cases that has decreased since the discovery of insulin. First meta-analysis of 22 studies conducted after the discovery of insulin reported 29.1 fatalities per 100 patients (Baker, 1936). This shows a dramatic decrease of 70% in terms of mortality rate. Number of deaths was further recorded to be reduced to 14.5 in 1958 when observed over a period of 5 years (Skillman *et al.*, 1958). However, a significant change has not been observed since then as mortality rate in 2005 was reported to be 11.8% of total DKA admissions (Umpierrez *et al.*, 2002; Ko *et al.*, 2005). It is notable that DKA is not an independent factor for patient's death. Associated complications of DM are also referred as reasons of mortality since most DM patients are accompanied by chronic co-morbidities. Among these associated complications, cardiovascular and renal complications are attributed to most of the deaths (Connell and Louden, 1983).

1.2.3 Epidemiology of Diabetic Ketoacidosis

Short after the discovery of insulin, DKA was referred as a metabolic disorder of patients with T1DM (Baker, 1936). It was considered that non-insulin dependant diabetes mellitus (NIDDM) patients are not prone to develop DKA (Fishbein and Palumbo, 1995) until DKA was observed more frequently in patients with T2DM (Westphal, 1996). Moreover, DKA occurring in newly diagnosed T2DM patients was found more severe than in previously diagnosed T2DM patients (Huri *et al.*, 2009). It

was also found that although the incidence of DKA in T2DM may seem less, DKA is, however, more or less observed equally in both arms since the number of T2DM patients exceeds T1DM patients. Moreover, obesity is considered among the greatest risks for the development of DKA along with alcohol and drug abuse (Umpierrez and Kitabchi, 2003).

1.2.4 Precipitating causes of Diabetic Ketoacidosis

Infection, non-adherence to DM management plan and new onset of diabetes are accountable for 70% of DKA cases. Non-adherence relates to deliberate omission of medicines intended for management of DM and, in terms of dietary plan and exercise, also includes patients' behavior towards the life style modification (Lutfey and Wishner, 1999). Around 90% of non-adherent patients show negligence to medication and/or lifestyle modification (Adibah and Ali, 1998). However, the studies reporting non-adherence of DKA patients toward DM management plan do not provide any data related to patients' adherence i.e. Morisky Scale (Weinert *et al.*, 2012). Similarly, respiratory and urinary tract infections account for up to 30 to 50% of all DKA episodes whereas gastrointestinal complication is accountable to 15% of them (Lebovitz, 1995; Umpierrez and Kitabchi, 2003). Apart for these, infection leading to DKA is also reported during post-operation time at the hospital. Moreover, catecholamines released due to infection induced stress also hinder peripheral glucose utilization and promote liver glucose production (McGuinness, 2005). Acute hyperglycemia in such scenario facilitates production of ketone bodies and hence, causes DKA (Grimaud and Levraut, 2001). However, an elevated white blood count (WBC) used to interpret infection in published reports might indicate dehydration instead of infection with out any data on

microbial smear (Huri *et al.*, 2009; Tan *et al.*, 2012). Likewise, new on-set of diabetes splits around 30% of DKA cases and it is well noted that these cases most commonly occur in T2DM patients (Kitabchi *et al.*, 2006). However, presentation of new diagnosis of DM as a DKA patient is noted by some researchers as atypical DM, and ketosis prone diabetes by others (Lebovitz, 1995; Kitabchi *et al.*, 2006). Hence, all these three factors remain debatable precipitating factors for a DKA episode.

Traumatic conditions such as head injury, stroke or myocardial infarction also contribute in development of DKA. It is believed that elevation in level of counter-regulatory hormones and decreased intake of water are the reasons for development of DKA (Laffel, 1999; Stewart, 2004; Kitabchi *et al.*, 2008b; Tu *et al.*, 2008). Drugs affecting normal carbohydrate metabolism i.e. thiazide diuretics, second generation anti-psychotics and corticosteroids also precipitate hyperglycemia and eventually, DKA (Kitabchi *et al.*, 2008b; Holt *et al.*, 2010; Hall and Guyton, 2011). This is especially observed in young patients with T1DM, and is exacerbated if eating disorder is found. Apart from these precipitating factors, 2 – 10% of DKA hospitalizations are recorded without any underlying cause (Umpierrez and Kitabchi, 2003; Stewart, 2004; Kitabchi *et al.*, 2006).

1.3 Pathophysiology of Diabetic Ketoacidosis: the cascade of events

Acute hyperglycemia triggers a cascade of events that lead to an episode of DKA as depicted in figure 1.1. Acute hyperglycemia is observed as a result of either decreased production of insulin by pancreatic β-cells or compromised activity of insulin receptor at cellular level. In some cases, both of these may occur simultaneously. This deregulation

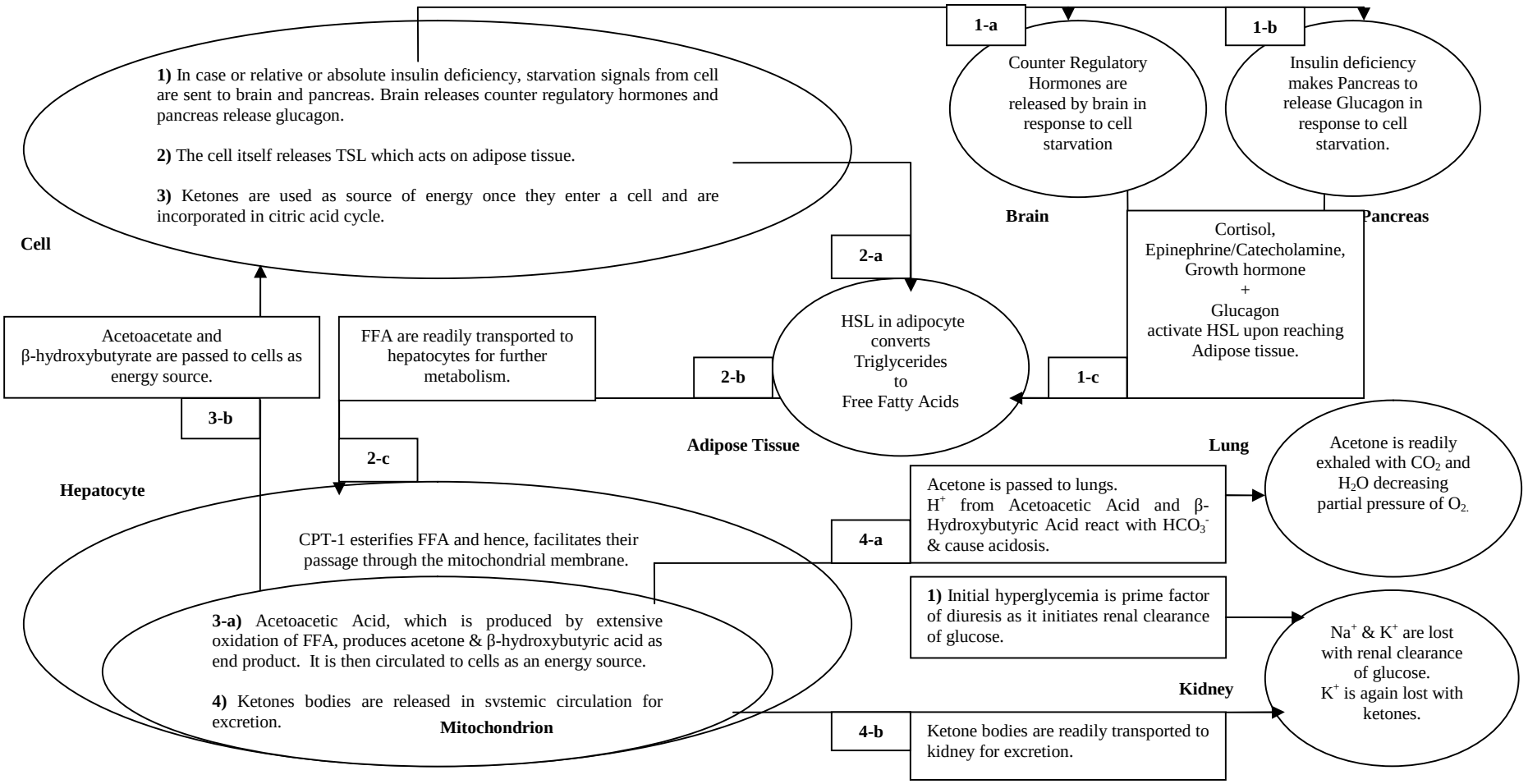

Figure 1.1 Cascade of events involved in DKA. 1) Insulin deficiency causes starvation in cell and hyperglycemia in extracellular compartment causing osmotic diuresis. 1-a) & 1-b) Brain and pancreas receive starvation signals from cell. 1-c) Counter-regulatory hormones and glucagon are released from brain and pancreas, respectively. 2) Cell produces tissue sensitive lipase (TSL). 2-a) Beside TSL, adipocyte itself produces hormone sensitive lipase (HSL). 2-b) Lipase converts triglycerides to free fatty acids (FFAs). 2-c) FFAs are transported to hepatocyte where carnitine palmitoyltransferase 1 (CPT 1) shuttle pass them in mitochondrion. 3-a) FFAs undergo oxidation to give Acetone and β-Hydroxybutyric acid (ketone bodies). 3-b) Ketone bodies are transferred to starved cell. 3) Starved cell consume ketone bodies as a source of energy by using them in tricarboxylic acid (TCA) cycle. 4) Ketone bodies are released to systemic circulation for excretion. 4-a) Acetone is exhaled and hydrogen (H^+), yielded from acetoacetic acid & β-hydroxybutyric acid, reacts with bicarbonate (HCO_3^-) and depletes buffer base to form water (H_2O) and carbon dioxide (CO_2) and hence, cause acidosis. 4-b) When in kidney, ketone bodies exhaust the water and electrolytes of the body while sodium (Na^+) and potassium (K^+) are extensively lost due to increased H^+ retention.

causes inadequate transportation of glucose from serum to the cell and develops a state of starvation at cellular level. In turn, body satisfies its energy requirements by utilizing adipose tissue which involves multiple metabolic pathways and results in acute metabolic derangement (Chiasson *et al.,* 2003; Charfen and Fernandez-Frackelton, 2005). Glucose is the chief source of energy and its concentration and utilization is regulated by insulin and glucagon. Insulin controls consumption of glucose and piles up excess of glucose in form of glycogen. On the other hand, when body is short of glucose, glucagon catabolizes glycogen back to glucose. This process is altered in two ways which trigger DKA: 1) In case of relative insulin deficiency, when available glucose is not able to enter a cell i.e. insulin resistance and 2) In case of absolute insulin deficiency (Holt *et al.,* 2010). As a reaction, glucagon, catecholamines and cortisol increase production of glucose via glycogenolysis and gluconeogenesis in liver (Foster and McGarry, 1983; Cahill, 2006; Barth *et al.*, 2007).

On the other hand, disturbed levels of insulin, glucagon and catecholamines hinder glucose absorption by peripheral tissues (Roden, 2004; Barth *et al.*, 2007). Increased hepatic glucose production and decreased peripheral glucose utilization cause pathogenic hyperglycemia in DKA. This hyperglycemia alters osmotic state and causes osmotic diuresis and dehydration All these factors decrease glucose clearance and further exacerbate hyperglycemia (Kitabchi *et al.*, 2001; Umpierrez and Kitabchi, 2003; Stewart, 2004).

An enzyme, hormone sensitive lipase (HSL), is activated by low level of insulin as shown in figure 1.2. Beside insulin, high levels of catecholamine and cortisol also

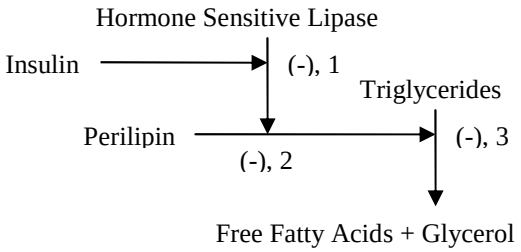

Figure 1.2 Natural barrier of insulin on ketosis. (1) Perilipin restrains production of free fatty acids from triglycerides. (2) Hormone-Sensitive Lipase (HSL) phosphorylate perilipin and thus, inhibits its function. (3) Activity of HSL is then controlled by insulin when it is dephosphorylated by insulin. Hence insulin, via natural mechanism, inhibits the production of ketone bodies.

contribute in activation of lipase (Laffel, 1999; Kraemer and Shen, 2002; Stojanovic and Ihle, 2011). HSL deactivates perilipin A and facilitates consumption of triglycerides to form free fatty acids (FFA). These FFA are converted to ketone bodies once they reach liver and are released into the circulation (Laffel, 1999; Stojanovic and Ihle, 2011). This process, ketogenesis, contributes to clinical condition of ketosis and is further influenced by the increase in glucagon levels. Within a hepatocyte, FFA in form of coenzyme A are readily transported across mitochondrial membranes with help of carnitine palmitoyltransferase (CPT) I as referred in figure 1.3.

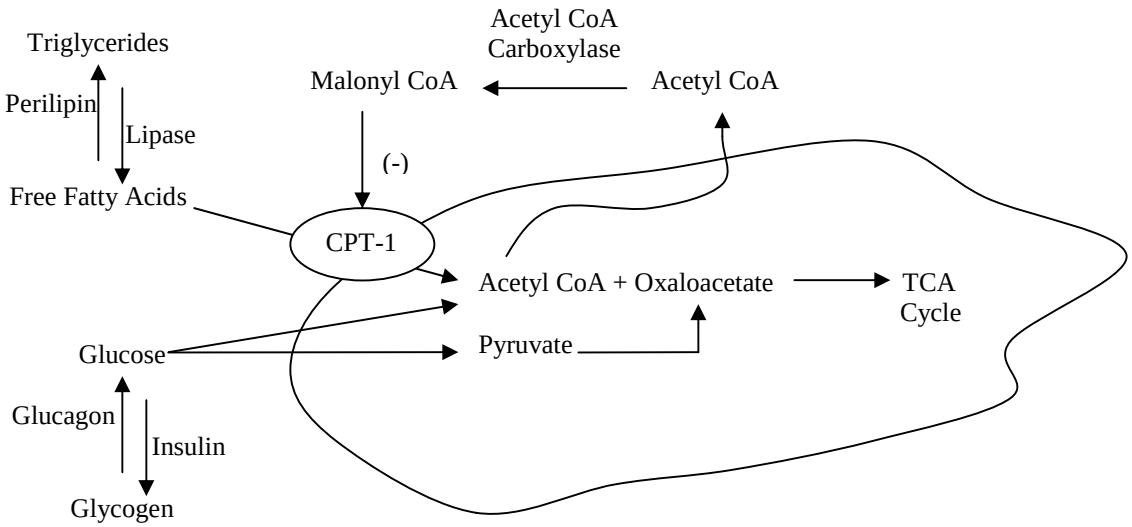

Figure 1.3 Natural role of insulin in liver. Acetyl CoA is formed by 2 processes; 1) β-oxidation of free fatty acids (FFA), and 2) Glycolysis. Acetyl CoA undergoes condensation with oxaloacetate, which is yielded from pyruvate during glycolysis, and is consumed in tricyclicacid (TCA) cycle. Mild fasting or fat rich diet, result in increased production of acetyl CoA which is diverted out of mitochondrion and is converted to malonyl CoA. Acetyl CoA carboxylase is chief enzyme for this conversion and insulin restricts its decomposition. Malonyl CoA inhibits carnitine polymaltoyl transferase-1 and thus, blocks the entry of FFA into the mitochondrion resulting in maintenance of homeostasis.

CPT I is activated by glucagon and it helps in esterification of coenzyme A into carnitine (Laffel, 1999; Casteels and Mathieu, 2003). Once inside, CPT II reverts it to fatty acyl coenzyme A which undergoes β-oxidation to produce acetyl coenzyme A (CoA). Acetyl CoA is then consumed in production of β-hydroxybutyric acid and acetoacetic acid in presence of nicotinamide adenine dehydrogenase (NADH) and is responsible for acidosis in DKA (Laffel, 1999; Umpierrez and Kitabchi, 2003).

Homeostatically, *p*H is maintained as these acids dissipate by donating a hydrogen ion which is readily accommodated by the plasma bicarbonate ions. However, production rate of these acids is much higher than the rate of their utilization in DKA and hence, these acids get accumulated in the body. As a result, *p*H of plasma shifts toward anionic system due to reduced availability of bicarbonate ions (Laffel, 1999; Stojanovic and Ihle, 2011).

1.4 Clinical presentation of Diabetic Ketoacidosis' patient: sign and symptoms in relation with cascading events

1.4.1 Hyperglycemia induced sign and symptoms

Persistent and acute hyperglycemia is foremost responsible for dehydration in DKA as illustrated in figure 1.4. Initially, excess glucose in the plasma encourages flow of water from the tissue toward extracellular space. It helps to maintain the osmotic pressure at expense of dehydration at cellular level. Furthermore, body tends to clear the excess of circulating glucose via kidneys and thus, water is lost alongside surplus glucose (Chiasson *et al.*, 2003; Umpierrez and Kitabchi, 2003). Meanwhile, ketones remain equally accountable for dehydration as they are also excreted via renal route. However,

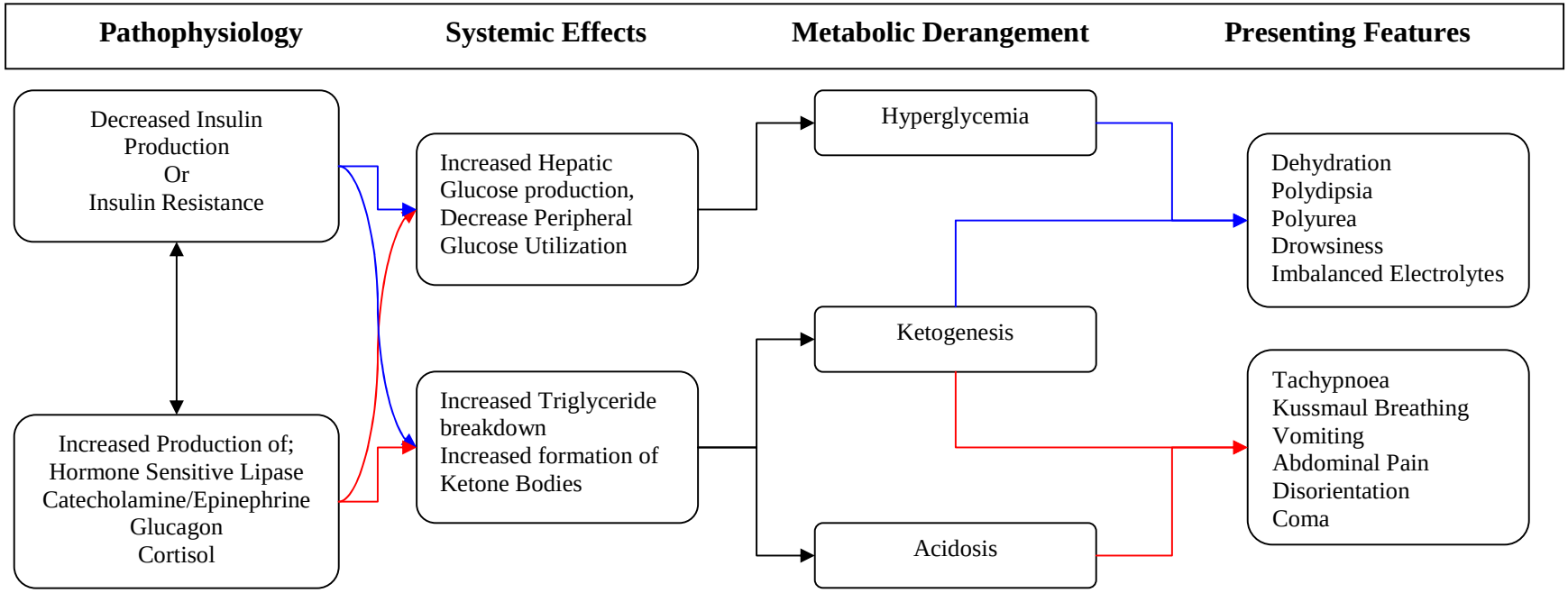

Figure 1.4 Signs and symptoms of DKA in relation with causative factor. Decrease in serum insulin concentration reduces peripheral glucose utilization and enhances insulin counterregulatory hormones (ICRH). ICRHs in turn increase insulin resistance. These factors collectively enhance hepatic glucose production and triglyceride breakdown in adipose tissue. Increased serum glucose concentration causes hyperglycemia whereas triglyceride breakdown causes ketosis and acidosis. Sign and symptoms associated with water content of body are influenced by ketosis and hyperglycemia. Ketosis, along with acidosis, also manipulate constitutional and central nervous system related sign and symptoms.

it is notable that by the time concentration of ketones reaches the minimal threshold of excretion, hyperglycemia has already had depleted adequate water content of the body. It is therefore observed that maintaining hydration during acute hyperglycemia results in mild to moderate episode of DKA rather than severe (Kitabchi *et al.*, 2006). Dehydration may take a couple of days to develop as water intake during the course of hyperglycemia is naturally increased. Together with dehydration, patient of DKA also complains about polyurea and polydypsia. All these are important sign and symptom which indicate acute hyperglycemia and dehydration (Chiasson *et al.*, 2003; Umpierrez and Kitabchi, 2003; Stewart, 2004).

1.4.2 Hyperkalemia induced sign and symptoms

During acute hyperglycemia, body tries to maintain the osmotic pressure at the expense of tissue and serum electrolytes. Since hyperglycemia also induces hyperkalemia, vomiting and diarrhea are hence, commonly reported complaints in DKA (Kes, 2001). Vomiting is a definite character of hyperkalemia whereas epigastric distress and diarrhea may be caused by gastric infection, gastroenteritis or hyperkalemia driven smooth muscle hyperactivity (Hoffman, 1950; Kes, 2001; Schaefer and Wolford, 2005). Furthermore, hyperkalemia gets intense as re-entry of extracellular potassium (K^+) within the cell is mediated by insulin, which is already below the baseline during an episode of DKA. Other factor that may partially worsen hyperkalemia is insensitivity of cells to catecholamine-driven potassium uptake (Kes, 2001). All these factors cause hyperkalemia which, beside the mild gastrointestinal effects, is also life threatening as it may cause shrinking of P-wave (diastolic arrest) and elevation of T-wave (ventricular fibrillation) (Kes, 2001; Stewart, 2004). Apart form gastric and cardiac effects,

hyperkalemia, though to a lesser extent, is also an important phase which may cause acidosis as it decreases secretion of H^+ and re-absorption of HCO_3^- in the renal tubular cells and may further exacerbate DKA (Schaefer and Wolford, 2005). However, initial hyperkalemia is readily converted into hypokalemia as the excess of potassium is excreted via kidney while clearing overload of glucose and ketones. General weakness is a definite character of hypokalemia and is often reported by patient of DKA (Hoffman, 1950; Hall and Guyton, 2011).

1.4.3 Ketosis induced sign and symptoms

Ketotic/acidotic breath, tachypnoea, and in severe cases Kussmaul breathing, are distinct features of DKA (Laffel, 1999; Umpierrez and Kitabchi, 2003). Excretory route for ketone bodies is via kidney in DKA and the hyperglycemia induced dehydration makes their clearance even difficult. Second route of excretion for ketone bodies is via respiration and once the acids (acetone specifically) reach lungs, they are readily exhaled and hence easily smelled in the breath of DKA patient (Laffel, 1999). Naturally, ketone bodies are weak acids and they quickly dissociate to give a H^+ ion. This H^+ ion is readily absorbed by the body's natural buffer system i.e. bicarbonates to form carbonic acid. Upon reaching the lungs, carbonic acid is promptly converted to CO_2 and H_2O which are then exhaled. In DKA however, respiratory system tries to be consistent with production of ketone bodies and clearance of carbonic acid and therefore, the rate of respiration is increased i.e. tachypnoea (Charfen and Fernandez-Frackelton, 2005; Umpierrez and Kitabchi, 2003). With the progress of DKA episode, it becomes difficult for body to cope with this equilibrium as bicarbonates are preoccupied with the overwhelming production of H^+ ion from ketone bodies. Meanwhile, metabolic acidosis stimulates

respiratory centre in the brainstem and peripheral chemoreceptors, and provokes hyperventilation. This causes a decrease in partial pressure of CO_2 which eventually drags the body toward an anionic system and further decreases the plasma *p*H (Chiasson *et al.*, 2003; Stewart, 2004; Yi *et al.*, 2010). The respiratory system gets compensated, breathing gets deep and laboring, and patient is observed as gasping for air. This phenomenon is known as Kussmaul breathing i.e. when blood gases have low partial pressure of CO_2 in concurrence with low bicarbonate due to forced increased respiration (Kitabchi and Wall, 1995; Chiasson *et al.*, 2003).

1.4.4 Acidosis induced sign and symptoms

Apart from respiratory distress, abdominal pain, which may occasionally be covering an acute abdomen, is a symptom often reported by patients with DKA (Dreschfeld, 1886; Baker, 1936; Umpierrez and Freire, 2002). Severe metabolic acidosis is usually associated with gastrointestinal signs which also include abdominal pain especially in patients with a history of alcohol or cocaine abuse. However, it is not certain that whether or not, abdominal pain is connected with the severity of hyperglycemia or dehydration as well (Umpierrez and Freire, 2002).

1.5 Laboratory values; Acid-Base and electrolyte homeostasis

1.5.1 Acid-Base homeostasis in Diabetic Ketoacidosis

Ketosis is a natural metabolic process that causes overproduction of β-hydroxybutyric acid and acetoacetic acid in DKA. Both of these acids dissociate readily, give a H^+ ion which binds with HCO_3^- at physiological *p*H and hence, cause a decrease in the level of HCO_3^- (Laffel, 1999; Chiasson *et al.*, 2003; Stojanovic and Ihle, 2011). Ketone bodies

themselves circulate in the anionic form and this causes a widening of anion gap. On average, the anion gap is 6 mmol · L^{-1} and lies within 3 – 11 mmol · L^{-1}. Anion gap is used as a measurement for metabolic acidosis in DKA and is based upon the difference between cations and anions measured by formula $Na^+ – (Cl^– + HCO_3^–)$ (Kitabchi *et al.*, 2006). Even with the substantial clearance of ketone bodies via kidney, high concentrations of acetoacetic acid and β-hydroxybutyric acid in DKA consume the bicarbonate ion and thus, widening the anion gap.

1.5.2 Electrolytes' homeostasis in Diabetic Ketoacidosis

The body is around 5 – 7 L deficient of total water in DKA which on average, is nearly 10–15% of body weight (Kitabchi *et al.*, 2006). Naturally, body is deficient of most abundant electrolytes i.e. sodium, chloride and potassium. During the early state of DKA, plasma values for sodium, potassium and chloride are elevated due to the initial intracellular-to-extracellular electrolyte movement. However, due to frequent loss of water and electrolytes via kidney, lower serum values of these electrolytes are detected by the time patient reports for medical advice. The minimum threshold value for these electrolytes is 135 mmol · L^{-1}, 98 mmol · L^{-1} and 3.5 mmol · L^{-1} respectively, whereas average shortfall for these electrolytes in DKA is usually 5–13 mmol · kg^{-1} body weight for sodium, and 3 – 7 mmol · kg^{-1} each for chloride and potassium (Jones, 1994; Kitabchi and Wall, 1995). As for sodium, serum sodium concentration is usually low to normal at the time of presentation and in some cases, hyperlipidemia may even cause hypernatremia at time of presentation (Umpierrez and Kitabchi, 2003). Similar characteristics are observed with chloride ion. Both these ions are found abundantly in human serum and may not cause serious effects if mild hypo– and hyper– values are

observed. These events however, do not appear easier while evaluating potassium as hyperglycemia prone shift of water forcefully evacuates potassium from intracellular to extracellular space and further subjects to renal clearance in the presence of hyperglycemia, acidosis and insulinopenia. Moreover, poor oral intake of potassium, vomiting and secondary hyperaldosteronism may further exacerbate potassium levels (Kes, 2001; Umpierrez and Kitabchi, 2003; Chiasson *et al.*, 2003).

1.5.3 Miscellaneous profiles in Diabetic Ketoacidosis

Beside the above mentioned biochemical profiles, some presenting characteristics are also considered in the continuum of DKA. Elevated HbA_{1C} is an indicator for poor adherence of patient with diabetic management and its use as a marker of non-adherence is helpful if there is no underlying cause found for DKA episode (Kitabchi *et al.*, 2006). Euthermia at the time of admission is also an indicator for patient not carrying any infection (Sawyer, 1903; Hockenhull *et al.*, 2012). However, this may not be used as a distinctive tool because hypovolemia may still cause hypothermia in presence of infection (Kitabchi and Nyenwe, 2006). Contrarily, though hypothermia is not a definite character of DKA, it may seem helpful to detect the progress in condition of patient as the patient with deteriorating condition may also develop hypothermia (Kitabchi *et al.*, 2006). Moreover, infection should only be ruled in/out by a proper microbiological profile as most of the DKA patients show leukocytosis at the time of admission. However, there may not be any pathological organism found in microbiological profiling (Stewart, 2004; Kitabchi *et al.*, 2006). Such phenomenon is observed due to severe dehydration secondary to hyperglycemia which may give false referral towards an infection (Bacon *et al.*, 1922; Umpierrez and Kitabchi, 2003).

1.6 Treatment goal for Diabetic Ketoacidosis management

Correction of dehydration, electrolyte imbalances, and hyperglycemia are of prime management importance for successful treatment of DKA. DKA patients undergo stress due to depleted fluid volume and metabolic derangement and hence, should simultaneously receive intravenous fluid hydration, electrolyte replacement and insulin administration (Stewart, 2004; Kitabchi *et al.*, 2006; Savage *et al.*, 2011). Any specific treatment should be decided later in accordance with precipitating cause. Frequent biochemical monitoring of patients should be carried in order to avoid any iatrogenic complication resulting from the treatment (Stewart, 2004; Savage *et al.*, 2011). Serum electrolytes, glucose and blood gases are considered important profiles to observe. Provided the etiology of DKA, treatment goals should be set on the following parameters;

1.6.1 Rehydration: as water moves toward the extra–cellular space because of increased glucose concentration. Moreover during the renal clearance of glucose, water and electrolytes are lost via urine. Loss of water may be observed around 100 ml · kg^{-1} of body weight (Chiasson *et al.*, 2003; Kitabchi *et al.*, 2006). Hence, rehydrating the patient enhances transportation of physiologically important ions within the body. It further improves the gaseous exchange in lungs and the renal function thereby resolving respiratory distress and facilitating excretion of metabolites and remains via urine.

1.6.2 Euglycemia: as an episode of DKA is triggered by hyperglycemia, hence its timely correction is important. While achieving euglycemia, insulin also redirects the deranged metabolic processes towards homeostasis. As depicted in figure 1.2 and 1.3,

insulin decreases catabolism of adipose tissue, inhibits CTP-1 shuttle and promotes glycogenesis thereby partially resolving crisis of ketosis and acidosis (Laffel, 1999; Casteels and Mathieu, 2003). Gradual decrease in the production of ketone bodies causes scarcity of acids. Hence, *p*H shifts toward normalization, level of bicarbonate is increased, and partial pressure of CO_2 and O_2 are improved (Lebovitz, 1995; Stewart, 2004).

1.6.3 Correction of electrolyte imbalance: as initial hydration only relieves the stress caused by the depletion of electrolytes during initial phase of DKA. However, insulin mediated re-entry of electrolytes form extracellular to intracellular space sets a new stress (Kes, 2001; Charfen and Fernandez-Frackelton, 2005). Close monitoring of the electrolytes and plasma components during initial phase of management is therefore equally mandatory. Sodium chloride in form of normal saline is used to maintain the volume of plasma. Occasionally, potassium, calcium and phosphates could also be added to avoid tetany and cardiac issues (Umpierrez and Kitabchi, 2003; Stewart, 2004).

1.6.4 Eradication of underlying cause: as urinary and respiratory tract infections are among precipitating causes for DKA in around 50% of cases (Lebovitz, 1995; Umpierrez and Kitabchi, 2003). Owing to the fact that leukocytosis with temperature spike may indicate infection, antibiotic should still rationally be given to DKA patient. Such impression of infection could be a mere aggregation of dehydration. Extensive care is required in DM patients with compromised renal and cardiac function and imbalanced electrolytes should be translated skillfully. Choice of medication is important in case of such co-morbidities which otherwise may give conflicting biochemical values. However,

swift improvement in hydration and glucose level enhance the chances of addressing underlying cause of DKA within 24hours (Kitabchi *et al.*, 2008b).

1.7 Treatment protocol for Diabetic Ketoacidosis management

There have been number of guidelines which encompass a treatment protocol for the management of DKA. Commonalities and differences among these protocols are discussed below.

1.7.1 Intravenous fluid expansion

Hypovolemia remains the initial goal in management of DKA. Fluid expansion restores vascular volume, enhances tissue perfusion and dilutes concentration of insulin counter-regulatory hormones (ICRH) and glucose. Moreover, it reduces adrenergic stimulation, DKA induced peripheral insulin resistance and haemoconcentration. It also improves exchange of ions and metabolites at tissue level and renal perfusion (Charfen and Fernandez-Frackelton, 2005). Commenced trails, meta analysis of such trails and recommended guidelines support the use of intravenous (IV) fluid replacement as a starter (Stewart, 2004; Barone *et al.*, 2007). However, there has not been a uniform formula to calculate the rate of administration of the IV fluid. It is a consensus that the rate of administration of IV fluid for initial couple of hours should be rapid in order to achieve hemodynamic stability and maintain cardiac output (Charfen and Fernandez-Frackelton, 2005). It should later be decreased to a rate where the total body water (TBW) deficit is compensated over 24h (Umpierrez and Kitabchi, 2003).

Normal saline (NS) is the recommended IV fluid to initiate resuscitation. Depending upon cardiac function and serum electrolytes, either 0.9 or 0.45% NS could be used. The TBW deficit for an average weight patient is around 5 to 8 liters ($0.6 \cdot \text{weight} \cdot [1\text{-}140 \cdot \text{serum sodium}^{-1}]$) (Stewart, 2004). Therefore, the rate of IV fluid infusion should be set so that 50% of TBW loss is recovered in 3rd part of the day and remaining, subsequently through the rest (Charfen and Fernandez-Frackelton, 2005; Kitabchi *et al.*, 2004; Bhave and Neilson, 2011). Some guidelines suggest that around 15 – 20 mL $\cdot$ kg^{-1} body weight $\cdot$ hour^{-1} of NS should initially be administered. It can then be reduced to 4 – 14 mL $\cdot$ kg^{-1} body weight $\cdot$ hour^{-1} (NICE, 2004; Kitabchi *et al.*, 2006; Embong and Yahya, 2009; Savage *et al.*, 2011). One to two liters of bolus IV fluid infusion is also recommended for rapid correction of hypovolemia. After initial infusion, this rate should be cut to half until the patient is found stable haemodynamically and subsequently, 0.45% NS should be used to cover the deficit of free water content of blood (Lebovitz, 1995; Kitabchi *et al.*, 2006). Other guidelines allow using 0.9% NS only if blood pressure is below 90 mmHg as in case of severe hypovolemia, there might be a greater loss of serum Na^+ ions. A complete biochemical profile of the serum electrolytes would be helpful to assess the use of IV fluid (Savage *et al.*, 2011). It is also recommended that once the value of corrected serum sodium has been retrieved, normal to high value of Na^+ should be reciprocated by using 0.9% NS and if found to be low, 0.45% NS should be administered (Lebovitz, 1995; Stewart, 2004; Kitabchi *et al.*, 2008b).

It is suggested that target for blood glucose level (BGL) should be set between 150 and 200 mg $\cdot$ dL^{-1} until the resolution of ketosis and acidosis. In order to avoid hypoglycemia during this phase, NS should be replaced with 5% dextrose. It could be

increased to 10 or 20% dextrose, provided that the BGL falls below 100 mg · dL^{-1} (Charfen and Fernandez-Frackelton, 2005). Use of 2 IV drips is suggested to avoid sudden change in BGL. While each bag should have same electrolyte concentration, one bag may contain dextrose in it (Grimberg *et al.*, 1999). Summarizing the consensus among the guidelines, notable points are that initial resuscitation should be at a fast rate; 0.45 or 0.9% NS could be used for resuscitation depending upon the cardiac and renal profile; NS should be replaced with dextrose so as to maintain the BGL.

1.7.2 Insulin therapy

Insulin therapy improves the BGL, inhibits gluconeogenesis and decreases lipolysis. It ceases the production of ketone bodies thereby reducing acidosis that occurs in DKA (Laffel, 1999; Stewart, 2004; Cahill, 2006). However, the time required achieving homeostatic values of glucose, bicarbonate and *p*H vary in each patient and depends upon the biochemical levels found at the time of admission and the precipitating cause. Physiological reduction of BGL by insulin is 80 mg · dL^{-1} · h^{-1}. Hence, the time to achieve targeted BGL of 200 mg · dL^{-1} can be calculated as (Barone *et al.*, 2007):

$$\text{Time in minutes} = \text{Initial blood glucose (mg} \cdot dL^{-1}) - 200/80$$

Estimated time for normalization of *p*H and bicarbonate levels is twice the time taken to attain the BGL of 200 mg · dL^{-1}. Comatose patients may regain consciousness following normalization of *p*H and bicarbonate. Reduction in plasma osmolarity should also be monitored. It should not exceed the rate of 3 mOsm · kg^{-1} of body weight · $hour^{-1}$ as it may trigger cerebral edema (Barone *et al.*, 2007). Some studies also suggest that in such

patients, BGL should not be reduced to less than 250 mg · dL^{-1} until the patient is lucid and oriented. Reason for this precaution is to avoid risk of cerebral edema and hypoglycemia that may remain unnoticed during such condition (Chiasson *et al.*, 2003; Trachtenbarg, 2005).

Use of low doses of insulin in management of DKA is supported by guidelines, as the slow delivery of continuous insulin infusion (CII) via IV route was found to be equally effective as the fast one (Kitabchi *et al.*, 2008a). Available trails and meta-analysis of such data also support use of CII (Stewart, 2004). Some guidelines suggest initial bolus IV insulin is recommended at a rate of 0.1 to 0.15 IU · kg^{-1} of body weight followed by CII at a rate of 0.1 IU · kg^{-1} of body weight · $hour^{-1}$ via infusion pumps (Kitabchi *et al.*, 2006; Savage *et al.*, 2011). Other guidelines suggest a higher constant infusion rate of 2 IU · $hour^{-1}$ (Embong and Yahya, 2009). In case of patients that are unresponsive to insulin and do not show any observable change in blood *p*H or anion gap, DKA management should be started with a bolus IV of 50 IU followed by the initial 10 to 20 IU as CII for some time (Fisken, 1999). NS or D5% could be used as a carrier of insulin for CII. However, the ratio of insulin solution should be set so that each 10 mL of CII may correspond to 1 IU of insulin (Barone *et al.*, 2007). Notably, should insulin be adsorbed by the rubber tubing of CII, 30 to 50 mL of early solution may be discarded (Magee and Bhatt, 2001).

During the first hour of CII, BGL should decrease by 50 to 70 mg · dL^{-1} and the insulin dose should be doubled hourly until BGL target is attained. This rate could be doubled as 0.2 IU (Kitabchi *et al.*, 2006) or 4 IU · $hour^{-1}$ (Embong and Yahya, 2009). It is also

suggested that IV bolus of 10 IU of insulin should be given after every hour until euglycemia is achieved (Kitabchi *et al.*, 2004). Nevertheless, all protocols recommend tight glycemic control within first 24 hours because it facilitates betterment in general condition of patient and avoids complications.

Intramuscular (IM) use of regular insulin as a substitute for CII is associated with several drawbacks. High rate of BGL fluctuation is observed following IM administration of insulin (Kitabchi *et al.*, 2001; Chiasson *et al.*, 2003; Stewart, 2004). Patients of DKA have moderate to severe dehydration and absorption of IM insulin is very low in peripheral tissues. Hence, it takes increased dose of insulin to achieve euglycemia. However, as hydration improves, absorption of insulin administered via IM route suddenly increases, which causes a sharp decline in BGL. Consequently, while using IM as the route for insulin administration, the rate at which insulin reaches the systemic circulation effectively is unpredictable. With BGL below 250 mg $\cdot$ dL^{-1} and normalization of blood pH, the CII should be replaced by IM insulin (Stewart, 2004). It is also suggested that rapid acting insulin should be divided in three doses over a period of 24 hours and long-acting insulin should be used at night to maintain a tight BGL. Such protocol is advised to be followed up to 72 hours after the discontinuation of CII (Barone *et al.*, 2007). Switching between the two routes should be done carefully. An initial dose of rapid-acting insulin is recommended 2 hours prior to the suspension of CII so that subcutaneous insulin adequately reaches the systemic circulation (Lebovitz, 1995). Patients with high risk co-morbidities and complications should be managed individually. A patient with pregnancy in first trimester or a renal failure patient may experience hypoglycemia. Contrarily, presence of infections, steroid usage and