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Review Article

**TREATMENT GOALS AND MANAGEMENT OF DIABETIC KETOACIDOSIS (DKA);
TIMELY ACTION NEEDED FOR DKA**

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ABSTRACT

Diabetic ketoacidosis (DKA) is an acute, well recognized and well studied complication of diabetes mellitus (DM). Its main characteristics are hyperglycemia, ketosis, acidosis and dehydration in case of profound insulin deficiency in diabetics. Earlier it was known to be a complication of patients with type I diabetes but now it occurs predominantly in type II diabetics. It is usually precipitated by infection of respiratory or urinary tract, insulin withdrawal due to decreased intake of food or taking a self implemented drug holiday and undiagnosed diabetes. One quarter of patients have no precipitating cause for DKA. Upon presentation, patient is severely dehydrated, hyperglycemic and has mild to moderate electrolyte imbalance. Goals set for the treatment are prioritize in order of hydration, euglycemia, correction of electrolyte imbalance and eradication of underlying cause. Preferred route of treatment is intravenous. Laboratory profiles are recommended to be monitored closely. With advancement of technologies, it is skillfully treated and complications are avoided well, yet incidence of DKA and mortality caused by DKA episode is increasing according to number. Also, the difference among the guidelines mentioned by experts is negligible. This leaves experts with no choice but to sit together and develop a consensus upon guidelines of diagnostic criteria, treatment goals and treatment protocol.

Key words: DKA, DM, Euglycemia, mortality

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INTRODUCTION

Diabetic Ketoacidosis (DKA) is a well known complication of Diabetes Mellitus. It is a serious, life threatening, severe form of metabolic decompensation and can cause wide variety of complications. Its main characteristics are dehydration, hyperglycemia, ketosis and acidosis. The patient presented with DKA may have blood glucose level from 11.1 to 55.6mmol/dl [1], arterial pH from 6.85 and below to 7.35 and bicarbonate from 3.5 to 19mmol/l [2]. These factors vary in each patient e.g. in pregnant women, patients with maintained renal function or who continued anti diabetic therapy at time of decreased oral intake may have a low level of glucose and a normal anionic gap [2]. Table 1 provided similar attitude among experts for the diagnostic criteria of DKA.

Table 1: Determining characteristics of Diabetic Ketoacidosis

Year	Reporter	Blood Glucose	+ve Ketone	pH	HCO ₃
1995	Kitabchi A [3]	> 13.9 mmol/l	Urine or Serum	< 7.3	< 15 mmol/l
1996	Rosenbloom A [4]	≥ 12 mmol/l	Urine or Serum	< 7.3	< 15 mmol/l
1997	Bell D [5]	> 13.9 mmol/l	Urine or Serum	< 7.3	< 15 mmol/l
2003	Chiasson J [6]	≥ 14 mmol/l	Urine or Serum	< 7.3	≤ 15 mmol/l
2011	Savage M W [7]	≥ 11 mmol/l	Urine or Serum	< 7.3	< 15 mmol/l

DKA was considered issue of type I diabetics earlier but now it is observed frequently in non-insulin dependent diabetics due to high prevalence rate of type II diabetes. In other words, the number of patients of DKA in each group is more or less same and now this concept is well recognized [8, 9]. The prevalence of DKA in developed country is 4.6 – 8 per 1000 diabetic person [3, 10]. But situation in developing countries is different. Up to sevenfold increase is observed in Korea over 20 years. Women and young adults are more prone to DKA than men [11]. In time treatment and diagnosis save 5% of patients which otherwise end in mortality. Mortality rate has significantly declined where it was around 31% in 1958 [12]. Age also affects mortality rate of DKA patients as mortality rate due to DKA is 12% for patients with age around 60 and 50% for patients with age 80 and above [12].

Pathophysiology of DKA

Plasma concentration of glucose is regulated by insulin and glucagon. Insulin is mainly responsible for utilization of glucose and it helps liver to pileup excess stock of glucose in form of glycogen. In absence of insulin, glucagon produces glucose from glycogen. However, this process is altered in DKA. In presence of enough insulin and glucose, the cells still lack the source of energy in turn causing release of glucagon in response to cell's starvation. Glucagon itself hinders further absorption of glucose by cells. Excess of gluconeogenesis and failure of glucose catabolism exacerbates hyperglycemia and cause disturbance in osmotic state [6]. On the other hand, as a protective mechanism, lack of insulin causes activation of lipase which releases free fatty acids (FFA) from adipose tissues. Upon reaching liver, these are utilized by liver as a source of energy and acetoacetic acid (AcAa) is formed as the end product. In presence of nicotinamide adenine dehydrogenase (NADH), this AcAa is readily converted to β -hydroxybutyric acid and acetone both of which are ketone bodies. Generally, these acids could be excreted in urine but the depletion of water reduces glomerular filtration rate and hinders the ketone clearance via kidney and volume of ketones in blood is increased [13]. Ketosis is the reason of ketotic or fruity breath. Furthermore, normally these acids dissipate rapidly leaving a hydrogen ion which readily is absorbed by the bicarbonate ion in plasma and hence pH is maintained. However in DKA, the rate of production of keto-acids exceed rate of their utilization and ends in accumulation of excess ketone bodies. This causes surplus quantity of hydrogen ion production which in turn reduces availability of bicarbonate ion, thus pushing the body to an anionic system. Carbon dioxide is ventilated causing decrease in partial pressure and further

decrease of plasma pH [4, 6]. This impact of ketone bodies on homeostatic pH of body is called acidosis.

Once plasma concentration of glucose increases, water is shifted to plasma so as to establish the osmolarity followed by electrolytes. Subsequent to the production of ketones, acids are transported inside the cells at cost of potassium which initially causes hyperkalemia. Potassium is prohibited from re-entering cell in absence of insulin and results in electrolyte imbalance. It is well understood that each 5.6mmol/l increase of glucose in blood level pushes the system to an osmotic stress of 5.5mOsm/kg [14]. Water moves from intracellular space to intravascular space to maintain the osmotic pressure and thus lead cells to further dehydration [2, 6]. Upon reaching the kidney, excess glucose excreted takes electrolytes, especially potassium, with it and hence induces osmotic diuresis. This eventually results in loss of water and electrolytes; sodium, chloride and potassium in particular. This is the reason of increased thirst, frequent urination and dry mouth and skin in patient of DKA. Hypovolemia causes decrease in renal function & pulse volume and increase in blood urea, creatinine and nitrogen [13].

Presentation, Signs and Symptoms

Compared with hypoglycemia, the signs and symptoms appear after some time in DKA. The slow and gradual onset of signs and symptoms is related to the accumulating effect of dehydration from osmotic diuresis and buildup of acid from ketone production. Mostly, reported symptoms by a patient are polyuria, thirst and polydipsia [3, 15]. Increase in plasma glucose concentration increases blood volume and renal excretion which results in polyuria and then, polydipsia. Other symptoms reported are vomiting and nausea because of initial hyperkalemia which causes irritability, restlessness, anxiety and muscle cramps. However, with the loss of fluid, hyperkalemia shifts to hypokalemia and symptoms reported are weakness, blurred vision abdominal pain, paresthesia, confusion and dizziness [3, 6].

Signs are very important to diagnose DKA patient. Due to the initial elevation and then loss of serum potassium there is a fluctuation in diagnosis. Hyperkalemia gives an elevated T wave on electrocardiogram and ventricular fibrillation and hypokalemia causes a premature ventricular ectopic beat and tachycardia [3, 4, 7]. Dehydration and hypotension are observable features of DKA. Other important signs are Kussmaul breathing and smell of acetone [15]. These classify DKA from other disorders such as Hyperglycemic, Hyperosmolar State and acute surgical abdomen (especially in children due to gastric distention or stretching of the liver capsule). Blood CO₂ reacts with H₂O and forms carbonic acid which upon reaching the lungs, is restored back to CO₂ and is exhaled. This alters gaseous equilibrium and pH of blood is disturbed due to acid load, hence increased rate of respiration and shortness of breath are observed as body tries to compensate the excess CO₂ via respiration [14].

In the period preceding DKA, there are events related to metabolic decompensation, such as polyuria, polyphagia, polydipsia, and fatigue. As DKA progress, nausea and vomiting may worsen dehydration. Headache, malaise, paresthesia and abdominal pain are also common [16]. With passage of time, altered level of consciousness and coma may occur but this complication is as low as 10% of patients may experience it. It is important to remember that existence of DM may not always be mentioned as DKA may be a case of new diagnosis for DM [1].

Physical examination reveals dehydration, dry mucous membranes, decreased skin turgor and tongue folds. Important markers could be tachycardia, ketotic breath and changes in respiratory rate. Initial tachypnoea is followed by Kussmaul breathing which progress to shallow breathing in severe cases. In clinical evaluation, signs and symptoms should be acquired along with laboratory profiles which may suggest possible triggering condition. They prove useful as they can be corrected hence facilitating recovery of DKA. Some factors may be said as poor prognosis, such as occurrence of complications in patients in extreme age, the presence of hypotension or hypothermia [17].

Different Entities of Metabolic Acidosis

Metabolic acidosis is divided in Diabetic Ketoacidosis (DKA), Hypoglycemic Hyperosmolar State (HHS), Lactic Acidosis which mainly comprise of Alcoholic Ketoacidosis (AKA) and Hyperchloremic Acidosis [18]. Diabetic ketoacidosis is case of absolute insulin deficiency or Insulin resistance resulting in ketosis. Hyperglycemic Hyperosmolar state is due to relative insulin deficiency without ketosis and involves catabolism of proteins. Excessive consumption of alcohol in a malnourished person may lead to alcoholic ketoacidosis. Hyperchloremic Acidosis is due to reduction in bicarbonate of body and may be drug induced as in case of carbonic anhydrase inhibitors [19], due to diarrhea or renal impairment.

Table 2: Difference among the laboratory values of Diabetic ketoacidosis, Hyperosmolar hyperglycemic state, Alcoholic ketoacidosis and Hyperchloremic acidosis

Parameter	Unit	DKA	HHS	AKA	HCA
Glucose Level	mmol/dL	≥ 14	≥ 34	≤ 14	> 13
Ketone (Serum/Urine)	Negative	+3 – +4	Trace	+3 – +4	Trace
Arterial pH	-	≤ 7.30	> 7.30	< 7.20	≥ 7.25
Serum Bicarbonate	mmol/L	≤ 15	> 15	< 20	< 20
Serum Sodium	mmol/L	< 134	> 146	136 – 145	136 – 145
Serum Potassium	mmol/L	≤ 4.5	< 3.9	≥ 5	> 5
BUN	mmol/L	$\geq 10 - 12.5$	$\geq 18 - 25$	$\geq 15 - 20$	Variable

DKA = Diabetic ketoacidosis, HHS = Hyperosmolar hyperglycemic state, AKA = Alcoholic ketoacidosis, HCA = Hyperchloremic acidosis, BUN = Blood Urea Nitrogen.

Upon presentation, most of the physical parameters overlap each other in the aforementioned classes. A patient with any of these disorders will acquire sign and symptoms of 1) Hyperglycemia, in terms of drowsiness, polyurea, polydypsia and thirst; 2) Dehydration, in terms of hypotension, weak pulse, lethargy, dry tongue and skin; 3) Acidosis, in terms of Kussmaul breathing, abdominal tenderness and alteration in conscious level. However, there is key difference while taking the initial notes from the patient or its caregiver. Initial laboratory results should then be used to ensure the type of complication, as mention in table 2.

Factors Causing Diabetic Ketoacidosis

Infection is the most prevalent factor for DKA and that is around 40%. Pneumonia and urinary tract infection are reason for around 30 – 50% cases. It was also found that DKA could also be precipitated by acupuncture and the organism found culprit was *Staphylococcus aureus* [20]. New onset of diabetes and misdiagnosis are prevalent factors as well. 23% of DKA patients are

found to be diabetic for the first time. Around 70% of DKA episodes are attributed to omission of insulin from the management therapy by the patient. Acute medical illness which may include myocardial infection, trauma, cerebral injury, acute pancreatitis and surgery may cause 10% of DKA cases [3]. 13% of patients have history of substance abuse, excess alcohol usage and cocaine [21]. Another factor, although uncommon, is any abnormality found in continuous subcutaneous insulin infusion delivery system.

Treatment Goals

Taking in account the metabolic and fluid volume stress experienced in diabetic ketoacidosis, treatment goals should be set on the following parameters;

1. Hydration;

Increased glucose concentration moves water toward the extra-cellular space and then with the renal clearance of glucose, it is lost via urine. This causes a severe dehydration of around 100 ml/kg of the body weight and thus hydration becomes a priority. Rehydration makes transportation of physiologically important ions throughout the body and facilitates the renal function i.e. excretion of metabolites via urine. It improves the gaseous exchange in lungs and help in resolving shortness of breath.

2. Euglycemia;

DKA cascade begin from hyperglycemia and hence its correction is important task to cover timely and while achieving euglycemia, crisis of hydration, ketosis and acidosis are resolved partially. When insulin comes in circulation, it eventually helps body to shift toward normal mechanism of metabolism. This results in decreased catabolism of adipose tissue. The gradual decrease in ketone bodies ultimately cut off the supply of acids which are responsible for ketosis and acidosis. Shift of pH toward homeostasis increases level of bicarbonate and this helps to resolves the issue of Kussmaul breathing.

3. Infection Eradication;

Around 30% to 40% of the cases of DKA are initially precipitated due to infection. Urinary tract infection and pneumonia are the leading causes for DKA along with some other infections such as fungal infection e.g. candidia. Hence the patient admitted for resolution of DKA having temperature spike should be given some antibiotic empirically. This is also required as medicinal therapy would help immune system to counteract the derangements. However, care should be practiced as diabetic patients are likely to have renal impairment as well.

Treatment Protocol

The present guidelines provided and followed by experts of diabetes and different schools of thought have a similar pattern to resolve DKA. Initial treatment to begin with is fluid replacement which itself will tend to decrease hyperglycemia and increase pH as well. The second important component is insulin which will help to have euglycemia and will promote utilization of glucose as a source of fuel and ultimately resolve ketosis and acidosis followed by potassium replacement. However, the use of bicarbonate and phosphate is not yet fully supported. The different protocols given by leading experts are summarized in table 3.

1. Fluid Replacement;

Hydration remains the most important step of treatment to maintain renal and cardiac output. It is also suggested that two way venous infusions should be started first. It reduces glucose concentration, suppresses adrenergic stimulation and DKA induced peripheral insulin resistance. It is observed that hydration makes cell more responsive toward insulin. It has a beneficial effect on osmolarity and it is well understood that high serum osmolarity causes decreased level of consciousness and alertness [3, 6, 22]. Earlier, it was found that slow rate of infusion is safer than fast infusion but guidelines followed today suggest that initiation of fluid replacement therapy should be started with 0.9% Normal Saline (NS) and an infusion rate of 20 – 30 milliliter per kilogram weight per hour. It should be then be titrated down to 10 – 15ml per kg per hour. It should also be switched to 0.45% NS if the patient is not hypovolemic. This should be followed in case if serum osmolarity is above 320mOsm/kg and/or serum level of sodium (Na^+) is above 155mEq/L. NS is replaced by 5% Dextrose (D5%) if glucose concentration is in lower category of hyperglycemia. Fluid correction should be made in less than 24 hours keeping in view heart and renal status.

2. Insulin;

Low dose of insulin is recommended to initiate management of hyperglycemia. It is proven that low dose of insulin is more beneficial to achieve euglycemia than high dose and complications are avoided as well. Starting dose for insulin is 0.1 – 0.15 units per kilogram weight as a bolus which could then be maintained to 0.1 units per kilogram weight per hour. This should decrease blood glucose level by 3 – 5mmol/l per hour [23]. In case it decreases less than 3mmol/l in first hour, dose of infusion should be doubled each hour. Once the blood glucose level is below 14mmol/l, infusion rate should be cut half of the initial dose and 5% dextrose should be given as IV fluid. The other important part is route of administration of insulin. The recommended route for administering insulin has been continuous intravenous infusion as observed in table 3. This helps in number of ways. Such low dose of continuous infusion of insulin will reduce the increased level of glucose at a steady rate for which the subcutaneous insulin is unable. It will not cause hypoglycemia as if the rate of blood glucose reduction is higher than suggested, the volume of infusion could be reduced. Also, by using continuous infusion, hypokalemia could be avoided which is important to handle because it causes cardiac arrhythmia. On the other hand, due to dehydration, subcutaneous insulin is not absorbed quickly. Hence excess dose of insulin is required to achieve the goal which with improvement of hydration may cause hypoglycemia. With shift of blood pH within normal range, insulin infusion should be stopped and switched to regular rapid acting insulin.

3. Potassium Replacement;

Beside the major depletion of potassium in the whole body, it is not uncommon to observe initial hyperkalemia in hyperglycemic patients. Initially, the serum concentration of potassium is increased so as to maintain the osmolarity but decreases as glucose is lost via urine. Potassium is rapidly depleted as episode of DKA progress.

	NICE 2004 [24]	Kitabchi 2006 [25]	JBDS 2011 [7]	USM Hospital Malaysia [26]
Fluid Replacement	1) 30ml / kg / h 2) 0.9% NS 3) BG 14 – 17mmol/l; a) In 6h → Glucose or Dextrose b) After 6h → 0.45% NS or 5% Dextrose 4) If BG < 4mmol/l → 0.45% NS + 10% Dextrose	1) Hypovolemia; a) Severe → 0.9% NS 1.0 l / h b) Mild → 0.45% NS 0.5 l / h 2) Sodium Concentration; a) High or Normal → 0.45% NS 500ml / h b) Low → 0.9% NS 500ml / h 3) BG < 11.2mmol/l → 5% Dextrose + 0.45% NS 250ml / h	1) Systolic Blood Pressure; a) < 90mmHg → 0.9% NS 500ml / 15 minute via Infusion Pump b) > 90mmHg → 0.9% NS 1000ml / h 2) Blood Glucose > 14mmol / l; a) 1000ml 0.9% NS + K ⁺ / 2h b) 1000ml 0.9% NS + K ⁺ / 2h c) 1000ml 0.9% NS + K ⁺ / 4h d) 1000ml 0.9% NS + K ⁺ / 6h 3) Blood Glucose < 14mmol / l a) NS + K ⁺ + 125ml 10% Dextrose / h	1) Severe Dehydration; a) 1 pint NS [*] + K ⁺ / 30mins for 1 hour b) 1 pint NS [*] + K ⁺ / 1 hour for 2 hours c) 1 pint NS [*] + K ⁺ / 2 hour for 4 hours d) 1 pint NS [*] + K ⁺ / 4 hour for 8 hours 2) Mild Dehydration; a) 1 pint NS [*] + K ⁺ / 2 hour for 4 hours b) 1 pint NS [*] + K ⁺ / 4 hour for 8 hours [*] $\leq$ 0.9% NS if Na $\leq$ 159mmol / l [*] $\leq$ 0.45% NS if Na $\geq$ 160mmol / l [*] $\leq$ 5% Dextrose if BG $\geq$ 10mmol / l
Insulin	1) Intravenous; 2) BG $\geq$ 14 – 17mmol/l → 0.1unit / kg / h 3) BG $\leq$ 4 – 14mmol/l → 0.05unit / kg / h	1) Intravenous; a) Regular 0.1unit / kg Bolus to begin with b) Regular 0.1unit / kg / h Continuous Infusion c) BG $\leq$ 11.2 → 0.05 unit / kg / h 2) Subcutaneous; a) Rapid Acting Insulin 0.3 unit / kg to begin with b) Rapid Acting Insulin 0.2 unit / kg / 2h c) BG $\leq$ 11.2 0.1 unit / kg / h 3) If BG not lowers 2.8 – 3.9mmol in 1 st h → Double the dose	1) Intravenous 0.1 unit / kg / h 2) Increase Infusion rate 1 unit / h if; a) Capillary Ketone not falling by 0.5mmol / l / h b) Bicarbonate not increasing by 3mmol / l / h c) BG not falling by 3mmol / l / h 3) Continue IVI till; a) Ketones < 0.3mmol / l b) Venous pH > 7.3 c) Venous Bicarbonate > 18mmol / l	1) Bolus insulin is not recommended 2) Start with 2 unit / h insulin infusion 3) Titrate dose as; a) BG decreases less than 2mmol / l / h, increase 2 unit / h b) BG falls around 2 – 4mmol / l / h, maintain dose until 10mmol / l c) BG decreases more than 4mmol / l / h, decrease 2 unit / h 4) Withhold insulin if serum K ⁺ $\leq$ 3mmol / l
Potassium Replacement	1) 20mmol in 500ml in each 500ml fluid bag	1) Urine Output ~ 50ml / h a) Serum K ⁺ < 3.3mEq / l i) Hold Insulin ii) Give 20 – 30mEq K ⁺ / h	1) K ⁺ > 5.5mmol / l → Omit 2) K ⁺ = 3.5 – 5.5mmol / l → 40mmol / l 3) K ⁺ < 3.5mmol / l → Consult	1) Add 0.5mg KCl in 2 nd hour until get laboratory results. Then follow; a) K ⁺ = 4.1 – 5.5mmol / l → 0.5gm KCl / pint

		b) Serum $K^+ > 5.3\text{mEq} / \text{l}$ i) Omit K^+ c) Serum $K^+ \sim 3.3 - 5.3\text{mEq} / \text{l}$ i) $20 - 30\text{mEq } K^+ / \text{l}$	Senior	b) $K^+ = 3.1 - 4.0\text{mmol} / \text{l} \rightarrow 1.0\text{gm KCl} / \text{pint}$ c) $K^+ = 2.5 - 3.0\text{mmol} / \text{l} \rightarrow 1.5\text{gm KCl} / \text{pint}$ d) $K^+ \leq 2.5\text{mmol} / \text{l} \rightarrow \text{Fast Correct}^*$ $^*_\sim 2\text{gm KCl in } 100\text{ml NS over } 1 \text{ hour}$
pH Management	1) Bicarbonate should only be administered if pH is 6.9 and below. 2) Phosphate is not recommended to be used.	1) pH < 6.9 a) $100\text{mmol NaHCO}_3 + 20\text{mEq KCl} / 400\text{ml H}_2\text{O} / 2\text{h}$ 2) pH = 6.9 – 7.0 a) $50\text{mmol NaHCO}_3 + 10\text{mEq KCl} / 200\text{ml H}_2\text{O} / 1\text{h}$ 3) Repeat every 2hour till pH > 7.0	1) Bicarbonate is not recommended to be used. 2) Phosphate should only be administered if skeletal muscle weakness or respiratory muscle weakness is experienced.	1) Consider giving 50ml 8.4% NaHCO_3 over 1 hour if; a) Arterial pH < 7.0 b) Arterial Bicarbonate < $10\text{mmol} / \text{l}$ 2) Repeat ABG 1 hour after completion of infusion 3) Repeat NaHCO_3 if pH still < 7.0

Table 3: Comparison among guidelines for the management of Diabetic Ketoacidosis.

This decrease in serum potassium level turns severe as the treatment is initiated. As soon as insulin is administered, potassium moves back from extra-cellular to intra-cellular fluid due to the insulin mediated potassium re-entry. It is also driven in by extra-cellular fluid expansion and osmotic diuresis. This situation needs to be monitored critically because potassium is necessary for normal physiological process of heart and circulation, muscle, respiration and central nervous system. Potassium replacement should be initiated as soon as the serum potassium value reaches $\leq 5\text{mmol/l}$ and the level of potassium should be maintained between 4 – 5mmol/l throughout the treatment [24 – 26]. Also, if serum potassium level is as low as $\leq 3.3\text{mmol/l}$, insulin should be withheld until this concentration is breached [27]. Such conduct is based upon the fact that hypokalemia may lead to life threatening complications like cardiac arrhythmias, cardiopulmonary arrest, respiratory muscle weakness which may progress to acute respiratory collapse.

4. Bicarbonates and Phosphates;

Although bicarbonate is required to resolve acidosis and there is a shortage of phosphate approximately up to 1 mmol / kg during DKA, administration of either bicarbonate or phosphate is controversial, even if their serum concentration is low, since it is assumed that the values will return to adequate levels with normalization of pH and increase in peripheral utilization of glucose. Acidosis increases renal retention of bicarbonate and an increase in peripheral utilization glucose increases cellular uptake of phosphate. Bicarbonate should be given only if pH is <7.0 because the administration of bicarbonate may; worsen hypokalemia; produce paradoxical acidosis of the cerebrospinal fluid in central nervous system; worsen intracellular acidosis (for increased production of carbon dioxide), cause hypocalcemia and hypoxia and slow down the decline of ketonemia [2, 3]. There is evidence that bicarbonate therapy may increase synthesis of ketone bodies, in opposition of effect of insulin. However, phosphates are also believed to significantly increase the pH which advocates infusion of bicarbonate as a priority. Phosphate on other hand shows improvement in mental function and lower mortality with replacement of phosphate [28]. It may restore 2, 3-diphosphoglycerate level and enhance oxygen dissociation and improve oxygen delivery to tissue. Possible indications for use of phosphate would be left ventricular dysfunction, lack of improvement in mental status despite improvement of acidosis, hyperosmolarity, anemia, respiratory depression or serum phosphate below 1 mg / dl. In case if replacement is inevitable, the proposed dose is up to 1.5 mEq / kg intravenously at 24 hours. However, attention must be paid to the risks arising from their use, such as the emergence of severe hypocalcemia with no obvious clinical signs of tetany. Beside the benefits cohorts state their use as un-justified [29].

5. Magnesium and Heparin;

Magnesium deficiency is associated with insulin resistance and increased platelet reactivity. Magnesium although may also be depleted in DKA, it is not know about the clinical relevance of its disability. If magnesium is $<1.8\text{ mEq / l}$ and there is tetany, magnesium sulfate should be administered as well. The recommended dose in these situations is 5 g of magnesium sulphate in 500 ml of 0.45% normal saline over 5 hours.

Dehydration being a complication of DKA results in decreased perfusion of vital organs and hence promotes coagulation processes, which may cause myocardial, respiratory, bowel, and brain infarctions. This reciprocates in morbidity and mortality in ketoacidosis associated

with thromboembolic disease in older patients. Use of low-dose heparin for prophylaxis is important therefore. It should be continued until patient is mobile with no evidence of dehydration or elevated serum osmolality. Unfractionated heparin or low molecular weight heparin are suitable forms to carry on treatment [2, 6, 24].

Complications Associated with Treatment

Time between the onset of DKA episode and beginning of treatment, presence of infection, age and proper diagnosis are key points which usually set the rate of mortality and morbidity. As the treatment is initiated, minor but fatal complications start coming up e.g. secondary infection, hyperchloremic acidosis [3, 13], hypoglycemia, hypokalemia and hypovolemia which are resolved conveniently [3]. However, some major complications are also observed which though have less number of episodes but are life threatening and include cerebral oedema and stroke, myocardial infarction and acute respiratory distress syndrome, the former having highest occurring rate.

Cerebral oedema is although rare but is most serious and often fatal. Around 1 in 100 patients develop oedema, 70% end up in death and 14% of rests are permanently impaired. It usually develops in 2 to 24 hours as treatment is initiated and is characterized by lethargy, headache, abnormal behavior, convulsion and finally progress to loss of consciousness [30]. The mechanism, still unknown however, is mostly discussed with respect to high infusion rate of insulin and fluid. When fluid replacement is started, the idiogenic osmoles, which are produced in response to hypovolemia as a natural mechanism inside the neuron, are unable to dissipate too rapidly as compared to insulin mediated entry of water. Thus both the major components to resolve DKA, themselves cause increased risk of cerebral oedema. Hence, it is suggested that both infusions should be infused at a gradual and low rate.

CONCLUSION;

Diabetic Ketoacidosis is a well recognized threat to diabetic patients. Early diagnosis and proper treatment facilitate quick recovery and help in avoiding the complication. A person having normal [1] or elevated level of glucose in blood presents ketone either in urine or serum with lowered blood pH and bicarbonate is susceptible of DKA. The goals set in mind while initiating treatment should be reconstitution of lost fluid as fluid and electrolyte replacement are of prime importance. Furthermore, reduction of glucose level in blood for which intravenous insulin should be administered instead of subcutaneous insulin to get maximum therapeutic outcomes and avoid complications [27 – 30]. Finally to get pH in normal range and if pH of arterial blood is below 7, infusion of sodium bicarbonate should be considered. One should be very cautious during the treatment of DKA as apart from the complications of DKA, treatment itself causes life threatening complications. Frequent patient monitoring and care for possible complications are essential.

FUTURE PROSPECT

Diabetic ketoacidosis is well controlled complication of diabetes mellitus in developed countries. The scenario is a bit different in developing countries and Malaysia, at this time, being part of aforesaid group, is accelerating itself to join developed nations by 2020. Recent studies in Malaysia show that the prevalence rate of DKA is high in Malaysia. It is however astounding that Ministry of Health (MOH) Malaysia does not have any guideline for management of DKA. Initially known as diabetic acidosis which had mortality rate of 100% in early 20th century, it has gained a successful treatment regimen with discovery of insulin but still it is action need of time to build a consensus among experts of endocrinology in Malaysia on what comprise of DKA, what should be the mind set while treating DKA and how to manage it? We, at School of Pharmaceutical sciences of Universiti Sains Malaysia, are retrospectively working to sketch the profile of patient of DKA and its management which afterwards will be helpful for researchers to develop a clear picture while they work out on prospect of guideline.

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