"A CLINICAL STUDY OF HYPERGLYCEMIC EMERGENCIES IN DIABETIC ADULTS PRESENTING TO A RURAL TERTIARY CARE CENTRE."

By

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IN

GENERAL MEDICINE

Under the guidance of

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A WORD OF GRATITUDE

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Dr. KISHORE B

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ABSTRACT

BACKGROUND:

Diabetic Hyperglycemic Emergencies are major reasons for Intensive care unit admissions, with mortality rates of up to 30%.[1] The two most serious hyperglycemic emergencies are Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State.[2] This study attempts to describe the clinical features, predictive factors ,laboratory correlates and outcome(in terms of recovery with or with out complications or death)of hyperglycemic emergencies in adults.

Diabetic ketoacidosis and Hyperglycemic hyperosmolar state are the most serious acute metabolic complications of Diabetes mellitus that may be life threatening if not properly treated.[3] These disorders occur in both type 1and 2 Diabetes mellitus. Prognosis of both the conditions worsen at the extremes of age ,especially in the presence of coma and hypotension.[4,5]

Diabetic ketoacidosis characterized by a triad of hyperglycemia, hyperketonemia, and metabolic acidosis, is one of the most common emergencies. [6,7] Hyperglycemic hyperosmolar state is characterized by hyperglycemia, dehydration without significant ketoacidosis.[8] Hyperglycemic emergencies caused either by increase in insulin needs[serious infections ,trauma, surgery where insulin resistance suddenly and dramatically increases] or decrease in insulin availability [deliberate discontinuation of treatment ,dysfunction of infusion systems , inappropriate changes of insulin doses or mistakes in insulin delivery].[8]

OBJECTIVES:

TO STUDY THE-

1.Clinical features of Hyperglycemic emergencies.

2.To identify factors predicting the outcome in terms of morbidity and mortality..

METHODS:

The following patients were included in the study:-

1. Diabetes mellitus type 1 and 2 presenting with Random blood sugar >250 mg/dl ,with either of the following-

-Presence of ketone bodies in the blood or urine ketone bodies and metabolic acidosis (pH <7.30 or HCO3 <15 meq/L)..

-Dehydration and serum osmolality >300mOsm/kg.

2. Patients of age above 18 years.

All consecutive patients presenting to R.L.Jalappa hospital emergency with above inclusion criteria fulfilled will be included in the study after taking informed written consent. Presenting complaints, examination findings, investigations will be noted and patients will be followed up from the time of admission till discharge/death..

RESULTS:

Incidence of Hyperglycemic emergencies among Diabetic patients was 8.22 %. Diabetic Ketoacidosis (DKA) was 44 % and Hyperglycemic hyperosmolar nonketotic state (HHS) was 56%. Majority of DKA cases were found in less than 30 years age group and HHS were common after 60 years of age . Among Hyperglycemic emergency patients studied 36% were women and 64% were men . Majority of women presented with DKA and majority of men presented with HHS. 30% had type 1 Diabetes Mellitus (DM) and 70% had type 2 DM. It was observed that DKA was more common among Type 1 DM and HHS was common among Type 2 DM.

Most common presenting clinical features were vomiting, Nausea, dehydration, altered sensorium, abdominal pain, tachycardia and acidotic breathing. All the symptoms were common among HHS patients except for acidotic breathing which was common with DKA patients. Mean duration of diabetes was high among HHS (15years) than DKA group(8 years). Commonest precipitating factor was infection followed by discontinuation of treatment . Amongst infections, Pneumonia was the commonest in DKA cases and Sepsis and Diabetic foot were the commonest among HHS patients.

The biochemical parameters noted in this study were those of hypokalaemia. hyponatraemia, hypernatraemia and azotaemia and hyperkalaemia. These abnormalities occurred more in people with HHS. Hyponatremia was the prevalent form of electrolyte abnormality in hyperglycaemic emergencies.Mean Serum Osmolality among DKA patients was lower than in HHS patients.

Some of the clinical and biochemical parameters which indicate bad prognosis were age, duration of diabetes, RBS at admission, PH ,Insulin requirement and comorbid conditions. Age and Duration were the predictors for Mortality in DKA patients and abnormal levels of Sodium (hypo and hypernatremia), Potassium(hypo and hyperkalemia) and increased Serum Osmolality levels were the predicting factors for mortality in HHS patients.

CONCLUSION:

Incidence of Diabetic Ketoacidosis(DKA) was 44 % and Hyperglycemic hyperosmolar non ketotic state(HHS) was 56% during this period. Majority of DKA subjects were found in less than 30 years age group and HHS subjects were common after 60 years of age. Majority of women presented with DKA and majority of men presented with HHS. It was observed that DKA was more common among Type 1 DM and HHS was common among Type 2 DM. All the symptoms were common among HHS patients except for acidotic breathing which was common with DKA patients. Commonest precipitating factor was infection followed by discontinuation of treatment. The biochemical parameters noted in this study were those of hypokalaemia. hyponatraemia, hypernatraemia and azotaemia and hyperkalaemia. These abnormalities occurred more in people with HHS. Hyponatremia was the prevalent form of electrolyte abnormality. Mean Serum Osmolality among DKA patients was lower than in HHS group. Cinical and biochemical parameters which may indicated bad prognosis were age, duration of diabetes, RBS at admission, PH , Insulin requirement and comorbid conditions. Age and duration were the predictors for Mortality in DKA patients and abnormal levels of Sodium (hypo and hypernatremia), Potassium(hypo and hyperkalemia) and increased Serum Osmolality levels were the predicting factors for mortality in HHS patients.

KEY WORDS: Hyperglycemic Emergencies, Diabetic Ketoacidosis, Hyperglycemic Hyperosmolar state.

LIST OF ABBREVIATIONS

AG	Anion gap
BUN	Blood urea nitrogen
Cl	Chloride
CPTI	Carnitine palmitoyltransferase
CRC	Central research centre
CVA	Cerebrovascular accident
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
ETOH	Ethyl alcohol
HCMA	Hyperchloremic metabolic acidosis
HCO_3	Bicarbonate
HDL	High density lipoprotein
HHS	Hyperglycemic hyperosmolar state
IDL	Intermediate density lipoprotein
IHD	Ischemic heart disease
IRI	Immunoreactive insulin
K	Potassium
L	Litres
mEq/L	Milliequivalence/ litre
Mos/kg	Milliosmoles/ kilogram
Na	Sodium
NEFA	Non-esterified fatty acids
NS	Normal saline
OHDS	Oral hypoglycemic drugs
PEPCK	Phosphoenolypyruvate carboxykinase
UKB	Urine ketone body
VLDL	Very low density lipoprotein
AGEs	Advanced glycosylated end products
VEGF	Vascular endothelial growth factor
CAD	Coronary Artery Disease
CVA	Cerbro vascular Accident
Yrs	Years

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INTRODUCTION

The prevalence of diabetes is on the rise all over the world. Hyperglycemic Emergencies are, therefore, a key component in clinical practice. A high index of suspicion for diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic states (HHS), which are the two of the most serious acute complications of diabetes, is essential for timely intervention and also for prevention of recurrent episodes.

These Hyperglycemic Emergencies continue to be important causes of morbidity and mortality among patients with diabetes inspite of major advances in the understanding of their pathogenesis and more uniform agreement about their diagnosis and treatment. They can occur in both Type 1 and Type2 Diabetes Mellitus. The annual incidence rate for diabetic ketoacidosis(DKA) estimated from population-based studies ranges from 4.6 to 8 episodes per 1,000 patients with diabetes.[1,2] Currently, diabetic ketoacidosis (DKA) appears in 4-9% of all hospital admissions among patients with diabetes.[3,4] The incidence of hyperosmolar hyperglycemic states (HHS) is difficult to determine because of the lack of population-based studies and the multiple combined illnesses often found in these patients. In general, it is estimated that the rate of hospital admissions due to hyperosmolar hyperglycemic states (HHS) is lower than the rate due to diabetic ketoacidosis (DKA) and accounts for <1% of all primary diabetic admissions.[3-5]

Mortality rates, which are <5% in diabetic ketoacidosis (DKA) and 15% in hyperosmolar hyperglycemic states (HHS),[3-5] increase substantially with aging and the presence of concomitant life-threatening illness. The prognosis of both conditions is substantially worsened at the extremes of age and in the presence of coma and hypotension.

REVIEW OF LITERATURE

HISTORICAL BACK GROUND

Clinical descriptions of polyuric states resembling diabetes mellitus have been described in the Ebers papyrus of Egypt in 15th century BC[6,7]. Ayurvedic literature from the times of Charaka and Sushrutha, the ancient Indian physicians identified two forms of "Madhu Meha" (honeyed Urine) in 400 BC[6]. One form associated with gluttony, obese build and indolence and the other characterized by thin build and early mortality recognized by these intuitive sages.

Important land marks in the history of diabetes

In 17th Century Thomas Willis of England[6-8] observed that some patient's Urine contain Sugar and in 18th Century Mathew Dobson[8] of England found that diabetic Serum Contain Sugar. John Rolo[6] of England in 1797 was one of 1st who coined the term diabetes mellitus. William Prout[9] of England described diabetic coma during 1810–20. Michael Chevreul of France noticed that the excess sugar in diabetes is glucose and Wihelm Petters of Germany demonstrated acetone in the urine of diabetic patients. Langerhans of Germany identified Pancreatic Islets in 1869. Adolf Kussmaul of Germany observed acidotic breathing in diabetic coma patient. In 1886, Dreschfeld[9] described DKA and HHNS (Hyper osmolar Hyperglycemic Non-ketotic Syndrome). In 1907, Jean de Mayer of Belgium postulated hypothetical glucose lowering hormone named insulin. In 1922 Banting[10], Best, Collip and Macleod isolated and clinically used insulin and later won Nobel prize for that memorable invention. Murlin JR of United States discovered and named glucagon in the year 1955. F.Sanger of England did sequencing of insulin and Roth et al. discovered insulin receptors in 1971. In 1977, Ulrich et al cloned insulin gene. In 1984 human

recombinant Insulin was available for clinical use and human insulin analogues in the year 2001[11].

Incidence and mortality

It is the commonest cause of death among patients with type 1 diabetes below 20 years of age[12]. Around 4% of all patients with diabetes and 20% of those with type 1 are admitted to hospitals with manifestations of ketoacidosis. Even if managed properly DKA can occur both in type 1 and type 2 diabetes patients. The mortality rate in patients with DKA is less than 5% in expert centers where as the mortality rate of hyper osmolar hyperglycemic state (HHS) is still remaining high around 15%[13]. The prognosis substantially worsened at the extremes of age. Prior to the discovery of insulin by Banting & Best in 1922, the mortality rate associated with episodes of DKA was almost 100%. By 1932 the mortality rate among 1007 patients with DKA reported by Bertram from a review of 25 different authors was down to 29%. Further reductions of mortality to 15% in 1955 and to 5% in 1960 were reported. This decline was thought to reflect the introduction of antibiotic therapy in the mid 1940s as well as other improvements in patient care, prompt therapy, observation, appropriate use of fluid and insulin brought down the mortality in 1950s. Recent reports of National Institute of Health (NIH) data analysis[14] suggests that between 1969 and 1973 the mortality rate for DKA in the patients with diabetes was 10%. After that the mortality rate steadily decreased and became 4-5%. It is mainly attributable to the immediate attention given to the patient in the emergency room.

DEFINITION OF DIABETES MELLITUS

Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. When fully expressed, diabetes is characterized by fasting hyperglycemia, but the disease can also be recognized during less overt stages, most usually by the presence of glucose intolerance. The effects of diabetes mellitus include long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, heart, and blood vessels. Diabetes may present with characteristic symptoms such as thirst, polyuria, blurring of vision, weight loss, and polyphagia, and in its most severe forms, with ketoacidosis or nonketotic hyperosmolarity, which, in the absence of effective treatment, leads to stupor, coma, and death. Often symptoms are not severe or may even be absent. Hyperglycemia sufficient to cause pathologic functional changes may quite often be present for a long time before the diagnosis is made. Consequently, diabetes often is discovered because of abnormal results from a routine blood or urine glucose test or because of the presence of a complication. in some instances diabetes may be apparent only intermittently, as, for example, with glucose intolerance in pregnancy or gestational diabetes, which may remit after parturition. In some individuals the likelihood of developing diabetes may be recognized even before any abnormalities of glucose tolerance are apparent. During the evolution of type 1 diabetes, for example, immunologic disturbances such as islet cell or other antibodies are present, and these may precede clinically apparent disease by months or even years.[15] In some families it is possible to recognize certain gene mutations that are strongly associated with certain forms of diabetes, such as variations in the glucokinase gene or hepatic nuclear factor genes that cause youth or early adult onset diabetes.[16] These genetic abnormalities are detectable at any time.

Although a number of specific causes of diabetes mellitus have been identified, the etiology and pathogenesis of the more common types are less clearly understood. The majority of cases of diabetes fall into two broad etiopathogenetic categories, now called type 1 and type 2 diabetes,[17,18]but the extent of heterogeneity among these types remains uncertain. Because of the increasing number of forms of diabetes for which a specific etiology can be recognized, the current clinical classification, proposed by the American Diabetes Association (ADA) in 1997[17] and adopted by the World Health Organization (WHO) in 1999[18] and that supersedes the previously internationally recognized 1985 WHO classification[19], now classifies diabetes according to both clinical stages and etiologic types . The clinical staging reflects that diabetes progresses through several stages during its natural history and that individual subjects may move from one stage to another in either direction.

CLINICAL STAGES:

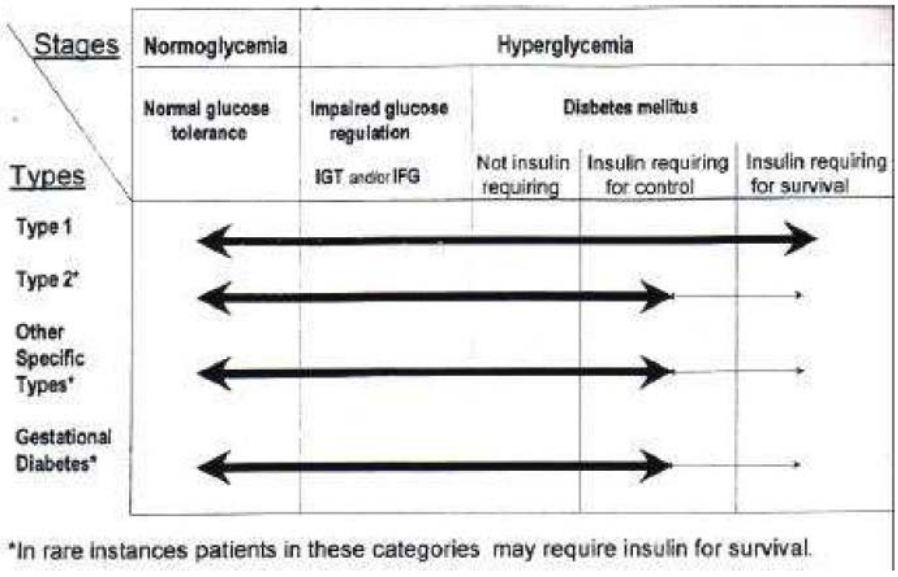

Fig. 1. Clinical Stages and etiologic types of diabetes

Table 1. Etiologic Classification of Disorders of Glycemia

- Type1 (β-cell destruction, usually leading to absolute insulin deficiency)
    A. Autoimmune
    B. Idiopathic
- Type 2 (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance)
- Other specific types
    - ✓ Genetic defects of β-cell function
    - ✓ Genetic defects in insulin action
    - ✓ Diseases of the exocrine pancreas
    - ✓ Endocrinopathies
    - ✓ Drug- or chemical-induced
    - ✓ Infections
    - ✓ Uncommon forms of immune-mediated diabetes
    - ✓ Other genetic syndromes sometimes associated with diabetes
- Gestational diabetes

Table 2: Other specific types of diabetes mellitus

Genetic defects of β-cell function Chromosome 20, HNF4 α (MODY1) Chromosome 7, glucokinase (MODY2) Chromosome 12, HNF1α (MODY3) Chromosome 13, IPF1 (MODY4) Chromosome 17, HNF3β (MODY5) Mitochondrial DNA, A3243G mutation Others	**Diseases of the exocrine pancreas** Fibrocalculous pancreatopathy Pancreatitis Trauma/pancreatectomy Neoplasia Cystic fibrosis Hemochromatosis Walcott-Rallison syndrome
Genetic defects in insulin action Type A insulin resistance Leprechaunism Rabson-Mendenhall syndrome Lipoatrophic diabetes Others	**Endocrinopathies** Cushing syndrome Acromegaly Pheochromocytoma Glucagonoma Hyperthyroidism Somatostatinoma Others
Other genetic syndromes sometimes associated with diabetes Down syndrome Friedreich ataxia Huntington disease Klinefelter syndrome Laurence-Moon-Biedl syndrome Myotonic dystrophy Porphyria Prader-Willi syndrome Turner syndrome Wolfram syndrome Others	**Drug- or chemical-induced** Nicotinic acid Glucocorticoids Thyroid hormone α-adrenergic agonists β-adrenergic agonists Thiazides Phenytoin Pentamidine Pyriminil (Vacor) Interferon-α Others
Uncommon forms of immune-mediated diabetes Insulin autoimmune syndrome (antibodies to insulin) Anti-insulin receptor antibodies "Stiff-man" syndrome Others	**Infections** Congenital rubella Cytomegalovirus Others

HNF4α, hepatic nuclear factor 4α; MODY, maturity-onset diabetes of the young; HNF1α, hepatic nuclear factor 1α; IPF1, insulin-promoting factor 1; HNF3β, hepatic nuclear factor 3β.

DEFINITION, CLASSIFICATION, AND CRITERIA

FOR DIAGNOSIS:

Diabetic Ketoacidosis (DKA) consists of the biochemical triad of hyperglycemia, ketonemia, and academia. As indicated, each of these features by itself can be caused by other metabolic conditions[20]. Hyperglycemic Hyperosmolar State" (HHS) has replaced the terms "hyperglycemic hyperosmolar nonketotic coma" and "hyperglycemic hyperosmolar nonketotic state" to highlight that alterations of sensoria may often be present without coma and the HHS may consist of moderate to variable degrees of clinical ketosis. The degree of hyperglycemia in DKA is quite variable and does not determine the severity of DKA. Serum osmolality has been shown to correlate significantly with mental status in DKA and HHS[20,21] and is the most important determinant of mental status, as demonstrated by several studies

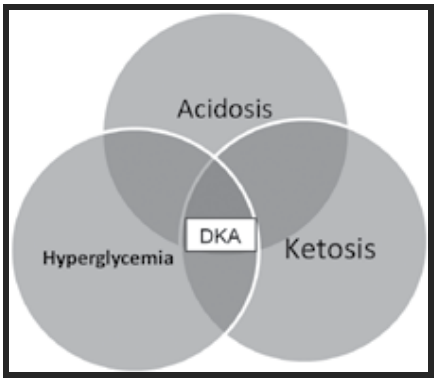

Fig. 3: The triad of DKA (hyperglycemia, acidemia, and ketonemia)and other conditions with which the individual components are associated. From Kitabchi and Wall [22].

Other hyperglycaemic states :

Diabetes Mellitus,Non-ketotic hyperosmolar coma

Impaired glucose Tolerance, Stress hyperglycemia

Other ketotic states:

Ketotic hyperglcemia, Alcoholic ketosis, starvation ketosis

Other Metabolic acidotic states

Lactic acidosis, hyperchloremic acidosis, salicylism, uremic acidosis,drug-induced acidosis.

Table 3. Causes of Hyperglycemic Emergencies

Common causes by frequency	Other causes	Selected drugs that may contribute to diabetic ketoacidosis
Infection, particularly pneumonia, urinary tract infection, and sepsis[4]	Acanthosis nigricans[6]	Atypical antipsychotic agents[12]
Inadequate insulin treatment or noncompliance[4]	Acromegaly[7]	Corticosteroids[13]
New-onset diabetes[4]	Arterial thrombosis, including mesenteric and iliac[5]	FK506[14]
Cardiovascular disease, particularly myocardial infarction[5]	Cerebrovascular accident[5]	Glucagon[15]
	Hemochromatosis[8]	Interferon[16]
	Hyperthyroidism[9]	Sympathomimetic agents including albuterol (Ventolin), dopamine (Intropin), dobutamin (Dobutrex), terbutaline (Bricanyl),[17] and ritodrine (Yutopar)[18]
	Pancreatitis[10]	
	Pregnancy[11]	

Precipitating Factors

One of the most common precipitating factors for DKA and HHS is infection in most populations of the world[23]. The most common infections are pneumonia and urinary tract infection which accounts for almost 30-50% of all cases seen. The other important cause is omission of insulin or undertreatment with insulin. Twenty percent of people may present with either DKA or HHS even without a prior diagnosis of diabetes. Acute medical illnesses as precipitating causes include trauma, alcohol abuse, pulmonary embolism, and myocardial infarction, which can occur both in type

1 and 2 diabetes. Various drugs which alter carbohydrate metabolism, such as corticosteroids, and excessive use of diuretics in the elderly may also precipitate the development of DKA and HHS.

In the Diabetes Control and Complications Trial, the incidence of DKA in patients on insulin pumps was about twofold higher than that in the multiple-injection group over a comparable time period.[24] This may be due to the exclusive use of short-acting insulin in the pump, which if interrupted leaves no reservoir of insulin for blood glucose control.

Omission of insulin due to psychological factors and poor compliance is an important precipitating factor for recurrent ketoacidosis. Factors that may lead to insulin omission in younger patients include fear of weight gain with good metabolic control, fear of hypoglycemia, rebellion against authority, and stress related to chronic disease.[25]

EPIDEMIOLOGY:

In the decade from 1996 to 2006, there was a 35% increase in the number of cases, with a total of 136,510 cases with a primary diagnosis of DKA in 2006—a rate of increase perhaps more rapid than the overall increase in the diagnosis of diabetes. Most patients with DKA were between the ages of 18 and 44 years (56%) and 45 and 65 years (24%), with only 18% of patients <20 years of age. Two-thirds of DKA patients were considered to have type 1 diabetes and 34% to have type2 diabetes; 50% were female, and 45% were male. DKA is the most common cause of death in children and adolescents with type 1 diabetes and accounts for half of all deaths in diabetic patients younger than 24 years of age.[26,27] In adult subjects with DKA, the overall mortality is <1% ; however, a mortality rate >5% has been reported in the elderly and in patients with concomitant life-threatening illnesses.[28,29] Death in these

conditions is rarely due to the metabolic complications of hyperglycemia or ketoacidosis but relates to the underlying precipitating illness.[30]

Mortality attributed to HHS is considerably higher than that attributed to DKA, with recent mortality rates of 5–20%.[31,32] The prognosis of both conditions is substantially worsened at the extremes of age in the presence of coma, hypotension, and severe comorbidities.[33]

Pathogenesis:

Etiology

Three major factors contribute to the pathophysiology, of DKA: insulin deficiency; increased levels of counter regulatory hormones; and dehydration. Proponents for the role of each factor have marshaled certain evidence from the literature and developed hypotheses for the pathogenesis, but until recently the paucity of data has made the development of a strong case for each hypothesis weak.

Insulin deficiency:

The hypothesis that insulin deficiency plays an important role in the pathogenesis of DKA has been difficult to clarify, since the measurement of immunoreactive insulin (IRI) in plasma may not adequately portray insulin secretion. Furthermore, some of the earlier studies demonstrating pancreatic secretory capacity in DKA[34,35]. Most studies have reported low to normal basal insulin levels in patients with DKA who had received insulin previously[36,37] .Baseline (fasting IRI levels usually range between 5 to 15 μ U/ml.

In nondiabetic subjects whose fasting blood glucose levels range between 70 to 115 mg/dl. Once such individuals are challenged with a glucose-containing meal

however their postprandial IRI increases five to sevenfold (to approximately 100μU/ml). In patients with DKA, however, despite having blood glucose levels 300mg/dl or higher, insulin levels are seldom above 15μ.U/ ml. Thus, insulin levels are very low and ineffective despite hyperglycemia,. However, since IRI is not a measure of the actual state of insulin secreation, a better method of determining the capacity for insulin secretion is necessary,such studies became available with the advent of the C peptide assay.

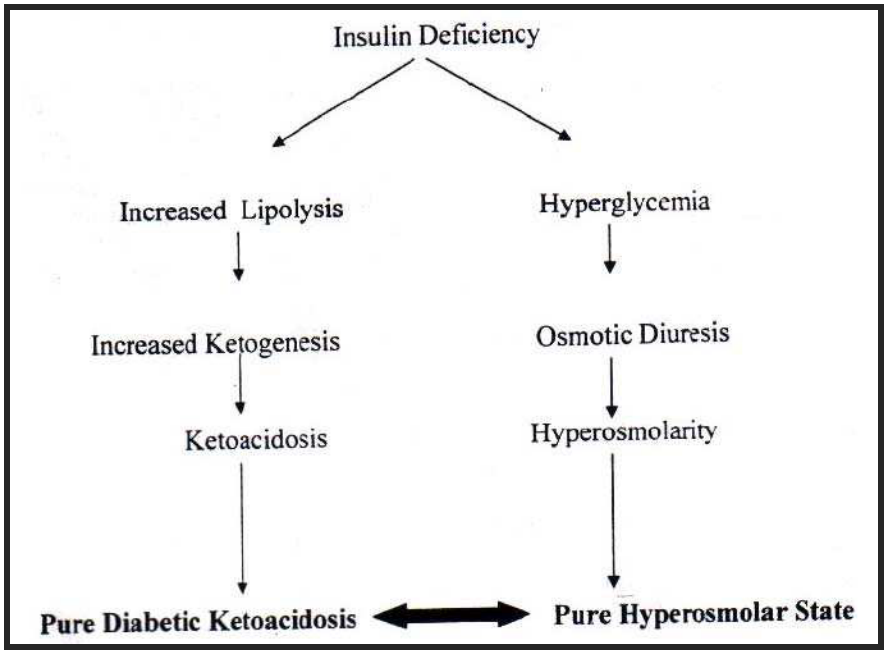

Fig 4.Hyperglycemic states

C-peptide is a 31-peptide component of proinsulin that is cleaved during the process of insulin biosynthesis and secreated in equimolar amounts with insulin.[38] One study showed baseline and hourly levels of C-peptide in 37 consecutive cases of patients with DKA who were admitted to the CRC from 1984 to 1985,[39] These studies revealed that on admission the average C-paptide value was 0.1 ± 0.05 nM and the average glucose level was 520 ± 30mg/dl. At recovery the C peptide level remained below 0.05nM. It is interesting that only 4 to 37 patients had C-peptide levels greater

than 0.2 nM, a finding suggesting that on admission the majority of these patients were insulinopenic with no significant pancreatic reserve either before or after recovery from DKA[40]

Increased counterregulatory Hormones:

It is well known that levels of counterregulatory hormones such as glucagons; catecholes, cortisol,[35,36,37,38] and growth hormone are increased and tend to return towards normal at recovery . This combined increase in levels of counterregulatory hormones may have an additive effect on glucose production and negative nitrogen balance in nondiabtetic obese subjects. In addition, since infection is the most common precipitating event in DKA, other factors may paly a role in insulin-dependent patients, infusion of counterregulatory hormones such as glucagons and growth hormone failed to bring about an elevation of levels of free fatty acids, ketone bodies, and glycerol in the presence of insulin. However, withdrawals of insulin during infusion of glucagons and growth hormone in combination with somatostatin promptly raised the level of these metabolites.[40] One factor that may contribute to a failure of elevation in levels of counterregulatory hormones may be the inability of certain patients with insulin –dependent diabetes mellitus (IDDM) of long duration to respond to stress by increasing levels of counterregulatory hormones.

Another study indicate that 30 to 40% of patients with IDDM of greater than 15 years' duration may have impaired glucagon and catecholamine response to stress, when counterregulatory hormone levels are low, the severity of ketoacidosis may be decreased.[40] It has therefore been suggested that although insulin deficiency is a crucial etiologic factor in the genesis of DKA, the severity of DKA may depend in part on the presence of "stress" hormones.[41]

Studies suggested that mild DKA can occur as a result of hypoinsulinemia in the absence of a significant elevaion of counterregulatory hormone levels.[40] The importance of increased levels of some counterregulatory hormones, however, in patients who develop DKA is apparent,however, in patients who develop DKA while receiving CSII during a stressful event. Such events may be seen in patients with IDDM who develop myocardial ischemia, intercurrent illness, or severe infection with concomitant elevation of counterregulatory hormones leading to increased free fatty acid and ketone body production, hyperglycemia, and ultimately ketoacidosis. Therefore, although elevations in counter-regulatory hormone levels are not essential to the development of mild ketoacidosis, they can exaggerate the state of acute metabolic decompensation.

Dehydration:

Dehydration is inevitably found in severe DKA and results from the osmotic diuresis of hyperglycemia, often being further complicated by fluid deprivation caused by gastrointestinal disturbances, the fluid deficit may be as great as 7L in severe DKA.

Adequate hydration is an important aspect of DKA therapy and that it can reduce the mortality rate dramatically.[42] Hydration has been shown to reduce hyperglycemia without altering acid-base balance.[43]since most of the glucose is disposed of in the urine.

Hydration also may improve ketoacidosis secondary to dilution of counterregulatory hormones.[40]

In summary, three factors-insulin deficiency, elevated levels of counterregulatory hormones, and dehydration-are important contributing factors in the development of DKA. Each can contribute to different degrees of decompensation of

the metabolic state, depending on the individual patient. The most severe cases of DKA are the result of a combination of prolonged deprivation of insulin, elevation of counter regulatory hormone levels and severe fluid deprivation.

ALTERATION OF INTERMEDIARY METABOLISM IN DKA

Glucose Metabolism :

Glucose ingestion, glycogenolysis, and gluconeogenesis provide three sources of glucose in the blood, whereas oxidation, lipogenesis, and glycogen synthesis provide the means of dissipating this substrate . Blood glucose levels are maintained within a very narrow range in normal individuals in a fed state, with particularly important control being exerted by insulin and glucagon. In the fed state, insulin is the major anabolic hormone responsible for the conversion of substrates into energy stores through its effects on insulin-sensitive tissues. Insulin assimilates amino acids into protein throughout the body, in liver and muscle, fatty acids into triglycerides in adipose tissue and liver, and glucose into glycogen in muscle and liver. DKA, on the other hand, is a catabolic state in which the major counterregulatory hormones (glucagon, catecholamines, cortisol, and possibly growth hormone), combined with various degrees of insulin deficiency, lead to an increase in gluconeogenesis (glucose production from noncarbohydrate precursors) and glycogenolysis.

Ketone Body Metabolism :

Insulin, the most potent antilipolytic hormone in humans, is effectively reduced during DKA in combination with a relative or absolute elevation in the levels of catabolic hormones such as catecholamines, glucagon, and cortisol. These events favor lipolysis with increased production of free fatty acids, leading to β oxidation by the liver and increased ketogenesis. Glucagon has a multifactorial effect on the

promotion of ketogenesis. Glucagon lowers the hepatic level of malonyl coenzyme A (CoA) by blocking the conversion of pyruvate to acetyl CoA through inhibition of acetyl CoA carboxylase.[40] the first rate-limiting enzyme in de novo fatty acid synthesis and production of malonyl CoA. Malonyl CoA usually inhibits carnitine palmitoyltransferase (CPTI), the rate-limiting enzyme for transesterification of fatty acyl CoA to fatty acyl carnitine, allowing further metabolism of fatty acid by β oxidation to ketone bodies in the mitochondria. Although it has been stated that reduction of malonyl CoA prevents the inhibition of CPTI and accelerates the production of β-hydroxybutyric acid and acetoacetic acid, a second mechanism was recently proposed. The KI of malonyl CoA for CPTI is increased in diabetes, leading to a decrease in the efficacy of inhibition of CPTI activity.[40] Glucagon also stimulates the hepatic level of carnitine by an unknown mechanism; this, together with an increase in CPTI and fatty acyl CoA leads to increased ketogenesis . In addition to the above mechanism, both cyclic adenosine monophosphate (cAMP) and glucagon in the presence of insulin deficiency exert a direct positive effect on ketogenesis that is independent of an increased substrate supply from adipose tissue (i.e., free fatty acids). Beside the ketogenesis in the liver, about 10 to 20% may occur in the kidney. Not only is production of ketone bodies increased in DKA, there is evidence that clearance of ketones is decreased. This decrease may be due to a decreased insulin level, an increased glucocorticoid level, and decreased ketone body utilization by peripheral tissues. Although some studies suggest both increased ketogenesis and decreased clearance of ketone bodies in DKA, at least one study using radioactive tracers indicated that clearance is normal in DKA. Acetone production is also variable in DKA and may contribute up to 50% of the acetoacetate produced.[40] Generally, the level of β-hydroxybutyric acid is about three times higher than that of acetoacetic

acid. β-Hydroxybutyric acid does not react with nitroprusside, whereas acetoacetic acid reacts avidly. Acetone also reacts with nitroprusside but to a much lesser degree. However, acetone does not have acidic properties, and because of its volatility, its level in the blood may vary according to the rate of respiration. Acetone also may serve as a gluconeogenic substrate in starvation and DKA. With improvement in DKA duringtherapy, conversion of β-hydroxybutyric acid to acetoacetic acid increases because of a higher oxidation state. During recovery, the molar ratio of acetoacetic acid to β-hydroxybutyric acid gradually increases. Thus, although both β-hydroxybutyrate and acetoacetate decline during therapy, the relative levels of acetoacetate increases. As expected, therefore, the nitroprusside reactions of urine and blood continue to remain at a plateau despite an improvement in metabolic state.

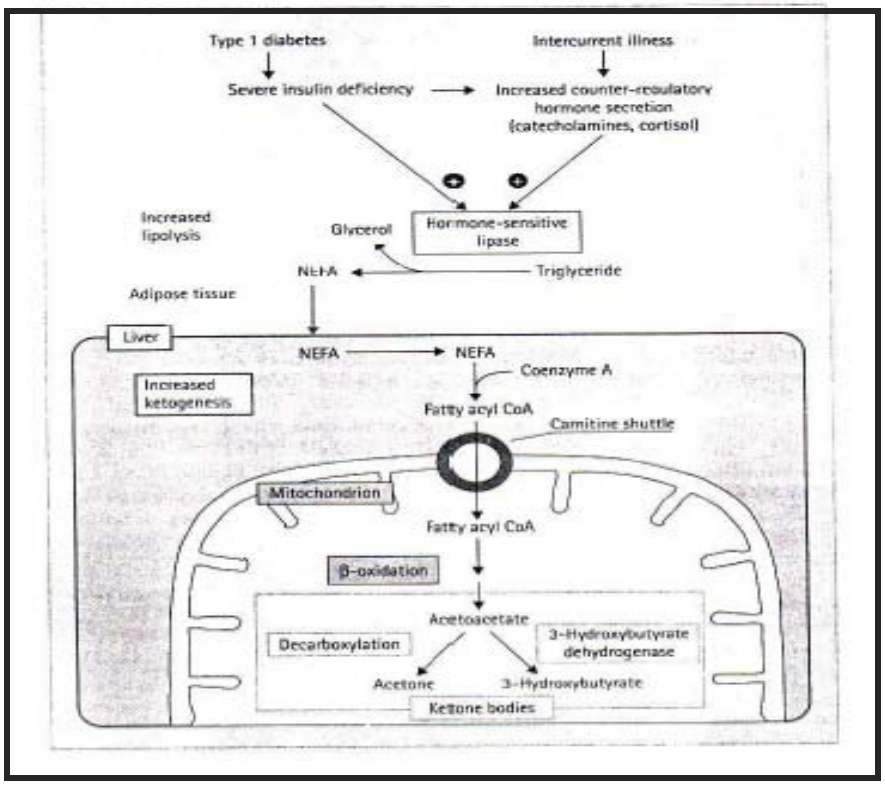

Fig 5 .Mechanisms of ketogenesis. NEFA non-esterified fatty acids

Protein and Amino Acid Metabolism :

Negative nitrogen balance is another hallmark of DKA. Insulin withdrawal results in the loss of 9 to 12 g of nitrogen per day followed by slow recovery during therapy.[40] In addition, levels of gluconeogenic amino acids (glutamine, alanine, threonine, serine, glutamate, glycine) decrease whereas levels of ketogenic amino acids (leucine,isoleucine, valine) increase during DKA. Both an increase in proteolysis and a decrease in protein synthesis have been suggested as reasons for these changes, but the detailed mechanism in humans has not been fully delineated. In experimental animal studies, acidosis appears to increase glucocorticoid production, which leads both to decreased protein synthesis and to increased nonlysosomal proteolysis. It is thus possible that in severe DKA, during which both glucagon and cortisol levels are elevated, synergistic effects of these two hormones enhance amino acidemia and sustain a negative nitrogen balance. In addition, under the influence of glucagon, alanine-the major gluconeogenic amino acid-is converted to glucose in the liver. Therefore, the plasma level of alanine is reduced in DKA as a result of increased gluconeogenesis.

Lipid Metabolism :

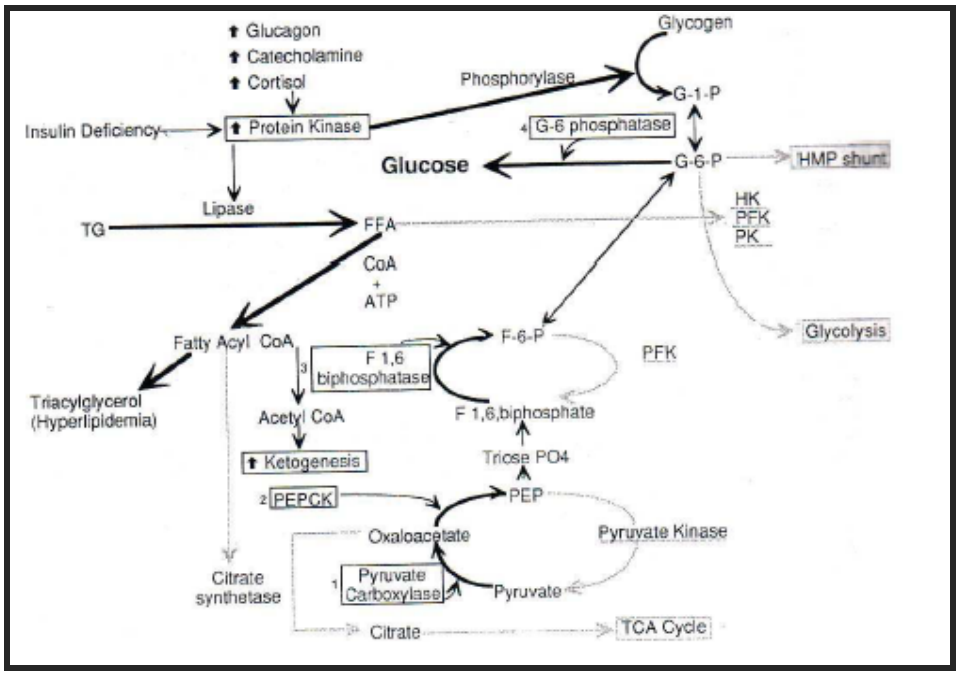

Fig 6. Proposed biochemical changes that occur during diabetic ketoacidosis

It has been known for many years that hypertriglyceridemia is frequently found in patients with severe, uncontrolled diabetes.[44] Increased levels of chylomicrons and verylow density lipoproteins (VLDL), demonstrated as lipemia retinalis, may be observed in severe DKA in the presence of increased lipolysis. Thus, in DKA there is apparent dichotomy of increased lipolysis and hypertriglyceridemia, but the level of serum cholesterol is relatively normal. The increased level of triglycerides is the result of an increase in the secretion of VLDL secreted by the liver in insulin deficiency, coupled with an increase in the level of free fatty acids, which leads to further synthesis of triglycerides. This increase in triglyceride levels occur despite the fact that VLDL production, relative to the level of free fatty acids, is decreased in patients with DKA as compared with that in nondiabetic subjects; however, an abudnance of free fatty acids in DKA ultimately leads to overproduction

of VLDL by the liver. Additional mechanisms responsible for hypertriglyceridemia in DKA may be decreased clearance of VLDL. With regard to lipoproteins in DKA, it is known that levels of intermediate density lipoprotein (IDL), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol are initially low in DKA. However, the level of HDL cholesterol rises with insulin therapy, whereas levels of IDL and LDL cholesterol do not. The mechanisms are not well understood. With the treatment of DKA with physiologic doses of insulin there is significant reduction in the level of apoprotein AI, as well as the ratio of apoprotein AI to HDL cholesterol. This suggests that insulin may decrease the secretion of apoprotein AI into the plasma or increase its catabolism.

Alteration of Biochemical Pathways :

As stated earlier, DKA is a catabolic state characterized by a net reduction of insulin action and an elevation in the concentrations of glucagon, catecholamines, and cortisol, changes leading to an increase in the cAMP-dependent protein kinase activity, which, through a cascade phenomenon, modifies metabolic pathways in three major insulin-sensitive tissues-muscle, fat, and liver-as follows. Increased lipolytic activity in adipose tissue leads to increased production of free fatty acids. As stated earlier, both increased substrate (free fatty acids) and increased levels of glucagon and cAMP, coupled with insulin deficiency, directly lead to increased ketogenesis, independent of the malonyl CoA mechanism. On the other hand, accelerated conversion of fatty acyl CoA to triacylglycerol, as well as decreased clearance of VLDL and chylomicrons, results in hypertriglyceridemia.Increased free fatty acid levels may also directly reduce glycolysis in the liver by decreasing the rate-limiting enzymes of glycolysis: hexokinase, phosphofructokinase, and pyruvate kinase. The high level of glucagon/insulin also may, through the activity of cAMP-dependent

protein kinase, decrease the hepatic level of fructose-1, 6-biphosphate. On the other hand, increased gluconeogenesis in DKA is achieved through activation of a series of rate-limiting enzymes-fructose-1,6-bisphosphatase, phosphoenolypyruvate carboxy-kinase (PEPCK), glucose-6-phosphatase, and pyruvate carboxylase-in the liver. PEPCK is particularly modulated by the inhibitory effects of insulin. In addition, glucagon-through cAMP production, the stimulation of cAMP-dependent protein kinase, and activation of phosphorylase-enhances glycogenolysis in the liver and the breakdown of glycogen to glucose-1-phosphate. Glucagon also enhances conversion of glucose-6-phosphate to glucose by activation of glucose-6-phosphatase in the liver[41]. This also reduces the flow of glucose-6-phosphate through the hexose monophosphate shunt. Thus, both glycogenolysis and gluconeogenesis are increased in uncountrolled diabetes and account for a major portion of the hyperglycemia in DKA . Furthermore, insulin deficiency in DKA results not only in increased hepatic output but in decreased uptake of glucose by insulin-sensitive tissues (muscle, fat, and liver), leading to further progression of hyperglycemia. These events are reversed with the institution of insulin therapy.

Renal Function and Acid-Base Balance :

DKA is characterized by increased renal excretion of glucose, ketone bodies, and nitrogenous compounds. There is also a nonspecific defect in tubular luminal uptake of low-molecular-weight proteins in DKA that is reversible within 10 to 15 days following metabolic recovery. A decrease in the plasma glucose concentration during hydration is caused primarily by renal glucose excretion and that the absence of maximal renal tubular reabsorption for both acetoacetate and β-hydroxybutyrate serves to explain in large urinary loss of sodium and potassium during DKA. The usual loss of water in DKA is approximately 5 to 8 L; with an average sodium and

potassium loss of about 400 to 700 meq and 250 to 700 meq, respectively. These losses represent a loss of water in excess of sodium, and therefore the fluid lost in DKA more closely resembles hypotonic saline solution than isotonic solution[45] the increase in plasma anion gap is due to the accumulation of ketone ions as a result of titration of protons from ketoacids by bicarbonate. However, this anion gap may not be correlated with serum bicarbonate. The normal anion gap (Na – Cl + HCO3) is between 8 and 16 meq/I. In DKA this gap is usually increased because of the presence of ketoacids as unmeasured anions. Thus, in DKA, acidosis ranges from anion gap acidosis to pure hyperchloremic metabolic acidosis (HCMA).

The degree of acidosis was independent of renal dysfunction and the severity of metabolic acidosis. However, the initial renal function appeared to be responsible for the variable retention of plasma ketones, i.e., the more severe the dehydration on admission, the greater the ketone retention with less prominent HCMA. The recovery from acidosis is slower in those patients admitted with HCMA. However, in those patients who developed HCMA 4 to 8 hours after the initiation of DKA therapy, the retention of chloride was in excess of the retention of sodium and of the excretion of ketones by the kidneys. The contributing factor in the development of HCMA may be a higher intravascular fluid volume and lower initial insulin level during initial therapy.[40]

Pathophysiological Basis of Clinical Presentation :

The effective reduction of insulin, the major anabolic and antilipolytic hormone, along with variably increased levels of counterregulatory hormones such as catecholamines, glucagon, and cortisol, brings about the metabolic derangements in DKA, in which the catabolic state predominates over the anabolic state. Lack of insulin promotes lipolytic activity and inhibits utilization of substrates by insulin-

sensitive tissues (i.e., conversion of glucose to glycogen, of amino acids to protein, and of free fatty acids to triglyceride). In the presence of a higher glucagon/insulin ratio and catecholamine levels, the reverse of the anabolic state prevails.

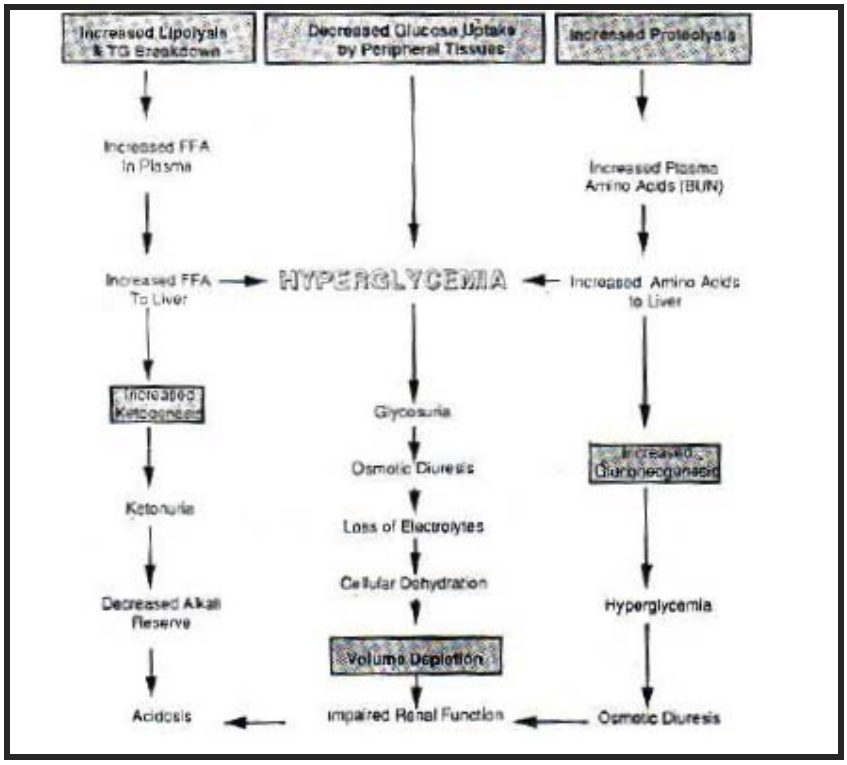

Fig 7. Altered carbohydrate, lipid, and protein metabolism in diabetic ketoacidosis and resultant water and electrolyte imbalances, impaired renal function, and acidosis resulting from insulin deficiency and increase in counterregulatory hormones

1. Catecholamines stimulate phosphorylase, which catalyzes the conversion of glycogen to glucose-6-phosphate by glyconeogenesis. Glucose-6-phosphate is converted to glucose by glyconeogenesis. Glucose-6-phosphatase in the liver.\
2. Catecholamines stimulate glycogenolysis in muscle, leading to the liberation of lactate rather than glucose since muscle lacks the enzyme glucose-6-phosphatase.

3. Catecholamines accelerate triglyceride breakdown to glycerol and free fatty acid in adipocytes. Glycerol provides the carbon skeleton for gluconeogenesis. Free fatty acids proceed through fatty acid oxidation and ketogenesis as previously described.

Free fatty acids also stimulate hyperglycemia through the gluconeogenic pathway.It is of note that in addition to providing substrate for ketogenesis in the liver through the action of glucagon and an increased glucagon/insulin ratio, increased levels of free fatty acids provide another source of triglyceride rich VLDL. Increased ketogenesis and decreased clearance of ketone bodies leads to ketonemia, which, when it surpasses the renal threshold, leads to ketonuria. The two major ketone bodies, β-hydroxybutyric acid and acetoacetic acid, are strong acids that are neutralized to β-hydroxybutyrate and acetoacetate, respectively, before excretion in the urine. This neutralization occurs at the expense of the bicarbonate reserve. This decrease in the bicarbonate reserve leads to manifestations of acidosis, as well as to further losses of sodium in the urine.

In the presence of acidosis, increased glucagon, and increased cortisol and in the absence of adequate insulin, proteolysis is increased and protein synthesis is decraesed. Such events transiently increase levels of both ketogenic and gluconeogenic amino acids.

The former are utilized in the liver for ketogenesis and the latter for gluconeogenesis in the liver or kidney under the influence of an increased glucagon/insulin ratio. The net result is increased hepatic production of glucose. Further hyperglycemia in DKA is brought about by decreased uptake of glucose in insulin-sensitive tissues, primarily in response to insulin deficiency but also because of the inhibitory effect of catecholamines and free fatty acids on glucose utilization by

peripheral tissues. Significant hyperglycemia above the renal threshold results in glycosuria and osmotic diuresis, with a loss of large amounts of fluid and electrolytes. Loss of fluid leads to polydipsia and polyuria. The increase in urinary loss of glucose leads to a loss of calories and ultimately to polyphagia. Thus, the catabolic state in DKA results in increased proteolysis, lipolysis, ketogenesis, gluconeogenesis, and glycogenolysis, changes that lead to acidosis, hyperglycemia, ketosis, severe dehydration, and transient impairment in renal function.These can be promptly reversed with appropriate hydration and physiologic doses of insulin, provided that therapy is initiated early enough

Table . 8 Regulation of Ketogenesis and Glucose Metabolism

	Ketogenesis	Gluconeogenesis	Glycogenolysis	Glycolysis	Glycogen Synthesis
Insulin	↓	↓	↓	↑	↑
Glucagon	↑	↑	↑	↓	↓
Cortisol	↑	↑	↑	↓	↓
Growth hormone	↑	↑	↑	↓	↓
Catecholamines	↑	↑	↑	↓	↓

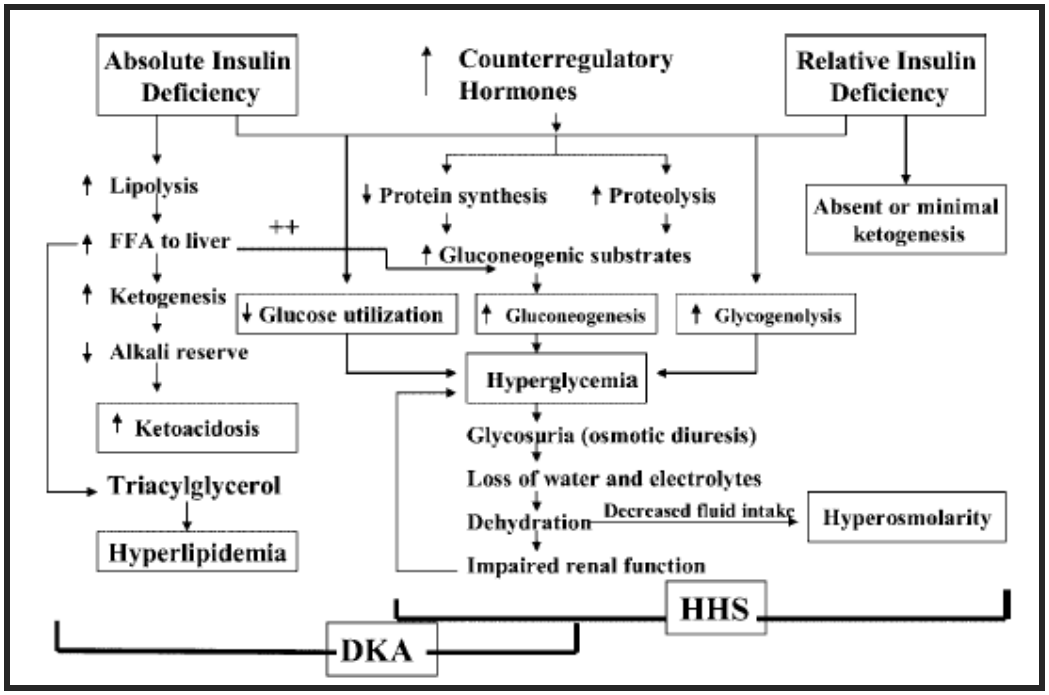

Fig 9.Pathogenesis of DKA and HHS: stress, infection, or insufficient insulin.

FFA, free fatty acid.

Increasing evidence indicates that the hyperglycemia in patients with hyperglycaemic crises is associated with a severe inflammatory state characterized by an elevation of proinflammatory cytokines (tumor necrosis factor and interleukin 6 and 8), C-reactive protein, reactive oxygen species, and lipid peroxidation, as well as cardiovascular risk factors, plasminogen activator inhibitor-1 and free fatty acids in the absence of obvious infection or cardiovascular pathology.[46] All of these parameters return to near-normal values with insulin therapy and hydration within 24 h. The procoagulant and inflammatory states may be due to nonspecific phenomena of stress and may partially explain the association of hyperglycemic crises with a hypercoagulable state.[47] The pathogenesis of HHS is not as well understood as that of DKA, but a greater degree of dehydration (due to osmotic diuresis) and differences in insulin availability distinguish it from DKA.[48] Although relative insulin deficiency is clearly present in HHS, endogenous insulin secretion (reflected by C-peptide levels)

appears to be greater than in DKA, where it is negligible. Insulin levels in HHS are inadequate to facilitate glucose utilization by insulinsensitive tissues but adequate to prevent lipolysis and subsequent ketogenesis.[49]

Table 5.CLINICAL FEATURES OF HYPERGLYCEMIC EMERGENCIES

Symptoms	Physical Findings
▪ Nausea / vomiting	▪ Tachycardia
▪ Thirst/polyuria	▪ Dry mucous membranes/reduced skin turgor
▪ Abdominal pain	▪ Dehydration / hypotension
▪ Shortness of breath	▪ Tachypnea / Kussmaul respirations / respiratory distress
Precipitating events	▪ Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen)
▪ Inadequate insulin administration	▪ Lethargy/obtundation/cerebral edema/possibly coma
▪ Infection (pneumonia / UTI / gastroenteritis / sepsis)	
▪ Infarction (cerebral, coronary, mesenteric, peripheral)	
▪ Drugs (cocaine)	
▪ Pregnancy	

Note : UTI, urinary tract infection.

Table 6 Biochemical profile in Diabetic Ketoacidosis (DKA) and Hyperglycemic Hypersmolar State (HHS) (Representative Ranges at Presentation)

Glucose, μmol/L (mg/dL)	13.9-33.3 (250-600)	33.3-66.6 (600-1200)
Sodium, meq/L	125-135	135-145
Potassium, meq/L	Normal to ↑	Normal
Magnesium	Normal	Normal
Chloride	Normal	Normal
Phosphate	↓	Normal
Creatinine, μmol/L (mg/dL)	Slightly ↑	Moderately ↑
Osmolality (mOsm/mL)	300-320	330-380
Plasma ketones	++++	+/-
Serum bicarbonate, meq/L	<15 meq/L	Normal to slightly ↓
Arterial pH	6.8-7.3	> 7.3
Arterial P_{CO2}, mmHg	20-30	Normal
Anion gap [Na – (Cl + HCO_3)], meq/L	↑	Normal to slightly ↑

DIAGNOSIS

History and Physical Examination

DKA usually evolves over a shorter period (usually less than 24 hours) than HHS, which tends to evolve over a few days. The symptoms of uncontrolled diabetes may be present for a number of days prior to the development of the acute metabolic decompensation. In some situations, e.g., in patients with type 1 diabetes who are using continuous subcutaneous insulin infusion pumps with regular insulin or short-acting insulin analogues, the symptoms of DKA can evolve much more rapidly-over 4 to 12 hours-if insulin delivery is disrupted. The pathophysiologic consequences of hyperglycemia, hyperketonemia, and insulin deficiency account for many of the classic symptoms and physical findings seen in DKA. High glucose levels lead to an osmotic diuresis, dehydration, and ultimately hypotension. The high ketone concentrations are responsible for the metabolic acidosis and also cause an osmotic diuresis because the renal threshold for ketones is low and ketones are osmotically active substances. The anionic charge on the ketones leads to excretion of positively charged ions, including sodium, potassium, calcium, and magnesium, to maintain electrical neutrality. The high solute excretion further impairs reabsorption of water from the renal tubule and loop of Henle, resulting in further loss of water and electrolytes. Insulin per se promotes reabsorption of water and sodium from the renal tubules. Insulin deficiency promotes further loss of water and electrolytes. Losses of potassium and phosphate are further exacerbated by the acidosis, which leads to loss of intracellular potassium and phosphate. This may complicate therapy. Ketone production by the liver leads to the metabolic acidosis. Hyperglycemia leads to an increase in serum osmolality, which in turn causes a further shift of fluid out of cells and leads to intracellular dehydration.[50]

Table 7: Average Fluid and Electrolyte Losses in Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Sodium	500 mEq
Chloride	350 mEq
Potassium	300-1000 mEq
Calcium	50-100 mmol
Phosphate	50-100 mmol
Magnesium	25-50 mmol

On the basis of the above pathophysiology, patients with DKA present with increasing polyuria and polydipsia, loss of weight, nausea, vomiting, increasing malaise, and dehydration. Patients with HHS tend to be more dehydrated at the time of presentation than patients with DKA. Abdominal pain is a common symptom in patients with DKA and may be due to the ketosis per se (with no evidence of intraabdominal pathology) or sometimes may be related to the cause of DKA. Fever is often present but may be absent even in the presence of infection because of the vasodilation that accompanies a metabolic acidosis. Patients may be alert at the time of presentation, but changes in mental status are common and may vary from drowsiness to coma. It is important to enquire about symptoms of the precipitating cause of the acute metabolic decompensation, such as symptoms of a urinary tract infection; the presence of cough, fever or chills; the recent introduction of new medications; or chest pain. All women of reproductive age should be asked about possible pregnancy and have a pregnancy test at the time of presentation. On examination, patients usually are dehydrated and have evidence of Kussmaul respiration if there is underlying acidosis. Assessment of the degree of dehydration is important. Decreased tissue turgor suggests 5% dehydration. An orthostatic change in pulse alone suggests that there has been loss of approximately 10% of extracellular

fluid volume (~2 L), whereas an orthostatic change in pulse and blood pressure (>15/10mm Hg) suggests a 15% to 20% fluid deficit (3 to 4L). Supine hypotension, when present, suggests either severe dehydration and a decrease in extracellular fluid volume of more than 20% or underlying sepsis. Assessment of degree of dehydration may be difficult in the elderly and those with underlyng autonomic neuropathy, who may have orthostatic hypotension at baseline. Fever may be present in those who have an underlying infection. The absence of fever, however, does not rule out infection-acidosis is associated with vasodilation and may lead to hypothermia. Hypothermia is an ominous finding andrepresents a poor prognostic sign. At the time of presentation, patients may be alert or have various degrees of change in mental status. Ranging from drowsiness to stupor to coma. The level of consciousness correlates more closely with the underlying serum osmolality than with the degree of acidemia. Up to 25% of patients with DKA complain of vomiting at the time of presentation. Some of these patients have acute gastritis and may be vomiting brown-colored fluid or blood when they are seen in the emergency department. Diffuse abdominal pain and tenderness may be presnt. It is important to differentiate this as a manifestation of DKA from other causes of acute abdominal pain that may have precipitated the acute metabolic illness. Neck stiffness may be present even in the absence of underlying meningitis. When underlying meningeal infection is a possibility, examination of the CSF is essential. Examination for signs of the precipitating illness is important; this includes thorough examination of the skin, throat, and chest for infection.

Laboratory Investigations :

Table 8 Diagnostic criteria for DKA and HHS

	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dl)	>250	>250	>250	>600
Arterial pH	7.25-7.30	7.00-7.24	<7.00	>7.30
Serum bicarbonate (mEq/l)	15-18	10 to <15	<10	>15
Urine ketones*	Positive	Positive	Positive	Small
Serum ketones*	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)$^{+}$	Variable	Variable	Variable	>320
Anion gap^{++}	>10	>12	>12	<12
Alteration in sensoria or mental obtundation	Alert	Alert/ drowsy	Stupor/coma	Stupor/coma

*Nitroprusside reaction method; $^{+}$Calculation: 2[measured Na (mEq/l)] + glucose (mg/dl)//18; $^{++}$Calculation: $(Na^{+}) - (Cl^{-} + HCO_3^{-})$ (mEq/l).

Initial laboratory evaluations of the patient with DKA must include plasma glucose, electrolytes, blood urea nitrogen (BUN) and creatinine, CO2, serum and urine ketones, calculation of the anion gap, arterial blood gas (for DKA), complete blood count and differential, and electrocardiogram. Cultures of urine, blood, and throat should be done if clinically indicated, and a chest radiograph should be obtained if there is any concern about an underlying cardiopulmonary problem. Measurement of glycosylated hemoglobin (HbA1c) may provide information about the underlying degree of metabolic control. The serum sodium level may be low or normal. It may even be elevated in patients who are severely dehydrated even though total body sodium is depleted. The acidosis leads to a shift of potassium out of the cells. Serum potassium levels at presentation may be high, normal, or low even though total body potassium may be depleted. Unless the initial serum potassium is elevated above 5.5 mEq/L or the patient is in acute renal failure or oliguric, potassium replacement is required when treatment is initiated, because resolution of the acidosis

will lead to cellular reuptake of potassium and the potential for hypokalemia and the risk of cardiac arrhythmia.

As noted above, the level of consciousness correlates more closely with serum osmolality than with pH.[50] Coma in an individual whose serum osmolality is less than 320 mOsm/kg warrants further evaluation for other causes of the coma.

Serum amylase and lipase levels may be elevated even in the absence of pancreatitis. In a recent study, serum amylase and lipase levels were nonspecifically elevated in 16% to 25% of cases of DKA.[51] The cause of this elevation is not known.

Table 9 :Laboratory Evaluation of Hyperglycemic Emergencies

Complete blood count

- Serum ketones
- Calculate serum osmolality and anion gap based on glucose and clinical findings
- Measure osmolar gap if ingestion of osmotically active substances other than glucose suspected.
- Urinalysis and urine culture
- Consider blood culture
- Consider chest radiograph
- Consider measuring HCG
- Acid-base assessment if indicated by clinical findings.
- HbA1c
- HCG, human chorionic gonadotropin; Hba1c glycosylated hemoglobin.

Table 10 :Commonly Used Calculations in the Evaluation of Patients with Severe Hyperglycemia

- Calculation of effective serum osmolality :

$$2\,[Na + K] + \frac{(\text{Glucosein mg/dL})}{18} + \frac{BUN}{2.8} + \frac{ETOH}{4.6}$$

- Calculation of the anion gap :

$[Na] - [Cl + HCO_3]$

- Correction of serum sodium :

$$\text{Corrected Na} = [Na] + 1.6 \times \frac{[\text{glucose in mg/dL}] - 100}{100}$$

- Uncomplicated metabolic acidosis :

Δ anion gap : Δ bicarbonate = 1

- Metabolic acidosis and metabolic alkalosis :

Δ anion gap : Δ bicarbonate = <1

BUN, blood urea nitrogen; ETOH = ethyl alcohol.

Although serum lipase measurement is more specific for the diagnosis of pancreatitis, this is not true in DKA, and elevations of either amylase or lipase to more than three times normal do not confirm the diagnosis of pancreatitis in these situations. It should be noted, too, that coexisting acute pancreatitis may be present in 10% to 15% of patients with DKA.[52] Leukocytosis may occur in DKA in the absence of infection, thereby making it more difficult to diagnose infection. The mechanism for this finding is not clearly understood.

Differential Diagnosis :

Other causes of ketoacidosis need to be considered when patients with diabetes present with ketosis. These include starvation ketosis and alcoholic ketoacidosis. Starvation does not usually cause acidosis. Pregnant patients are more likely to develop ketoacidosis due to starvation because pregnancy is associated with an accelerated state of starvation and lipolysis and ketogenesis may be more

accentuated and start within 6 hours of fasting.[53] Alcohol may be associated with ketoacidosis. In this condition, plasma glucose levels are not always elevated. Serum ketones as measured by the nitroprusside reaction are not always significantly positive, because there is increased production of β- hydroxybutyrate in alcoholic ketosis and this is not measured in the nitroprusside reaction.

Other causes of an anion gap metabolic acidosis need to be considered in the differential diagnosis of DKA. These include lactic acidosis, uremia, and drugs (salicylates, methanol, ethylene glycol, and paraldehyde).

Unusual Clinical and Laboratory Findings :

Although the majority of people presenting with DKA and HHS have plasma glucose levels above 250 mg/dL, some patients may have lower plasma glucose levels at the time of presentation. "Euglycemic ketoacidosis" was originally described in situations in which the plasma glucose concentration was less than 300mg/dL and the plasma bicarbonate concentration was 10 mEq/L or lower, but serum glucose levels lower than this have been reported. Euglycemic ketoacidosis has been reported in patients using continuous subcutaneous insulin infusion pumps, which contain short-acting insulin (regular or short acting analogues lispro or aspart). In these patients, interruption of insulin delivery results in the rapid development of ketosis, as patients become profoundly insulin deficient within 2 to 4 hours of cessation of insulin delivery. Euglycemic DKA has also been reported during pregnancy and in subjects using "conventional" insulin regimens.[54] In these patients, the excretion of larger amounts of glucose in the urine or lower rates of hepatic glucose production may account for the relatively "normal" glucose concentrations. These patients are usually

alert and if they are not vomiting, can sometimes be managed with frequent administration of subcutaneous insulin rather than intravenous insulin infusions.

Table 11: Differential Diagnosis of Ketosis and Anion Gap Acidosis

	Starvation ketosis	Pregnancy ketosis	Diabetic ketoacidosis	Alcoholic ketoacidosis	Lactic acidosis	Uremic acidosis	Salicylate intoxication	Methanol or ethylene glycol ingestion
PH	Normal	Normal or decreased	Decreased	Decreased	Decreased	Slight decrease	Decreased or increased	Decreased
Plasma glucose	Normal	Normal or increased	Increased	Normal	Normal	Normal	Normal	Normal
Anion gap	Normal	Normal to increased	Increased	Increased	Increased	Increased	Increased	Increased
Serum ketones	Slight increase	Slight increase	Increased	Normal to increased	Normal to slight increase	Normal	Normal	Normal
Serum osmolality	Normal	Normal	Increased	Normal	Normal	Increased	Normal	Increased markedly measure serum levels

Serum ketones may be negative in some situations, such as alcoholic ketoacidosis or DKA associated with hypoxia. In these circumstances, the nitroprusside reaction fails to detect β-hydroxybutyrate, which is the dominant ketone present. Under "normal" conditions, the ratio of β-hydroxybutyrate to acetoacetate is 3:1. This increases to 8:1 in alcoholic ketoacidosis or DKA associated with severe hypoxia.

Serum creatinine may be spuriously elevated in DKA; the ketones interfere with the measurement of creatinine when measured by the alkaline picrate (Jaffe) assay, resulting in a falsely elevated level.[55] Treatment of the ketoacidosis leads to resolution of the problem.

Although the most common acid-base disturbance seen in DKA is an uncomplicated, partially compensated metabolic acidosis, other abnormalities of acidbase status may occur[56] These can range from a hyperchloremic acidosis (associated with no anion gap) to a metabolic alkalosis associated with vomiting. In the typical patient with DKA, the increase in the anion gap (ΔAG) is usually

equivalent to the decrease in the serum bicarbonate concentration (ΔCO2). The ratio of the ΔAG to ΔCO2 (Δ:Δ ratio) is equal to 1 in uncomplicated DKA. Hyperchloremic acidosis may occur at any stage during the course of DKA but is more likely to occur during treatment with fluids that include saline. Loss of ketoanions in the urine is associated with a decrease in the serum bicarbonate concentration. During treatment, large amounts of fluid and NaCl are administered. Chloride is reabsorbed to maintain electrical neutrality. This may lead to excess chloride and a hyperchloremic acidosis, which is associated with a normal anion gap. The Δ:Δ ratio in this situation is not equal to 1.44 Excessive vomiting in DKA may lead to excess loss of hydrogen ions and a metabolic alkalosis, which is characterized by a decrease in the chloride concentration and a normal serum bicarbonate level. Once again the Δ:Δ ratio is not equal to 1.

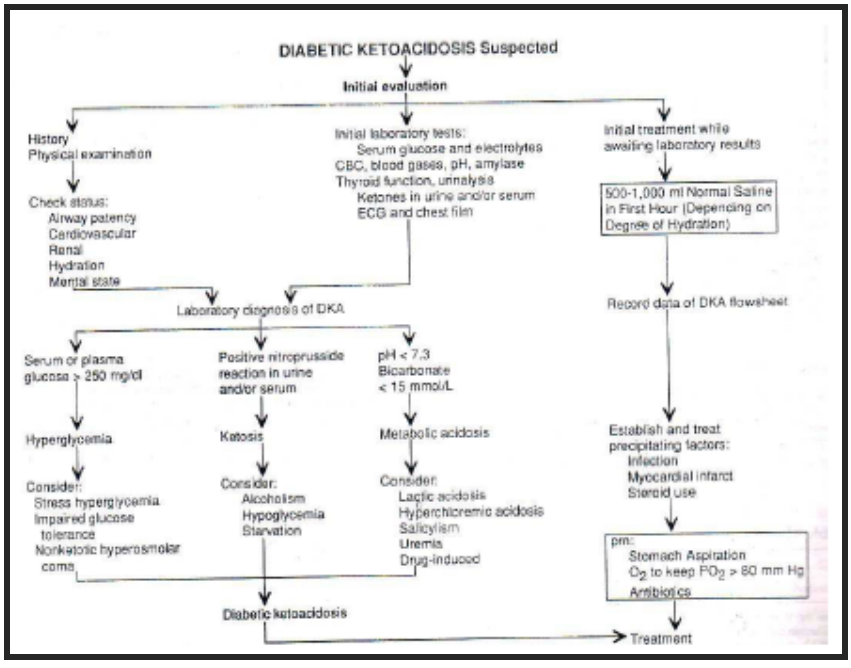

Fig 8. Flow diagram depicting the work-up of a patient with suspected diabetic ketoacidosis (DKA).

TREATMENT:

Treatment of both DKA and HHS is based on correcting the underlying pathophysiologic defects, correcting the fluid and electrolyte imbalance, normalizing the blood glucose, correcting the acid-base disturbance, treating the precipitating cause, and determining what factors need to be addressed to prevent a recurrence. The fluid and electrolyte abnormalities are treated with saline, water, and potassium; the hyperglycemia is treated with insulin; and the acidosis is treated with insulin and sometimes bicarbonate.

Fluids :

Fluid and electrolyte losses are considerable in most patients with DKA or HHS. Initially, fluid replacement is aimed at correcting the volume deficit rather than restoring serum osmolality to normal. Restoration of intravascular volume lowers blood sugar (independent of insulin) and decreases the counterregulatory hormones, improving insulin sensitivity. Normal saline (osmolar concentration, 308 mOsm/kg) is recommended for initial fluid therapy. Even though this fluid is isotonic, it is relatively hypotonic compared with the osmolality of the patient's serum. If the patient is in shock or has an inadequate blood pressure response to normal saline, colloid may sometimes be used together with normal saline.[57] The initial rate of fluid administration depends on the degree of volume depletion and the patient's underlying cardiac status and ranges from 2 to 4 L during the first hour of therapy to 1L per hour (15 to 20mL/kg per hour). There is some debate concerning the optimal time to change from normal saline to 0.45% normal saline. Once the corrected sodium is normal or elevated and most of the initial volume deficit is replaced, most clinicians would change treatment to 0.45% normal saline. The rate of fluid replacement must take into account ongoing urinary losses and be administered at a rate that will correct

the fluid deficits in 24 hours.[58] Osmolality should be corrected at a rate of approximately 3 mOsm/kg per hour. Once serum glucose has dropped to less than 250mg/dL, dextrose-containing fluids should be used (5% dextrose in 0.45% saline) and the insulin infusion rate adjusted to maintain blood glucose levels in the 120 to 180mg/dL range.

Table 12: Suggested Fluid Replacement

Administer NS as indicated to maintain hemodynamic status, then follow general guidelines :

- NS for first 4 hours.
- Consider half NS thereafter.
- Change to D5 half NS when blood glucose ≤250 mg/dL

Hours	Volume
1st half-hour to 1 hour	1 L
2nd hr	1 L
3rd hr	500 mL-1 L
4th hr	500 mL-1 L
5th hr	500 mL-1 L
Total 1st 5 hr	3.5-5 L
6th-12th hr	250-500 mL.hr

May need to adjust type and rate of fluid administration in the elderly and in patients with congestive heart failure or renal failure. NS, normal saline; D5, 5% dextrose in water.

Fluids are administered to children at a rate of 10 to 20 mL/kg per hour during the first hour of treatment, usually not exceeding 50mL/kg during the first 4 hours of therapy.

The rate of fluid replacement is calculated so that the fluid deficit is replaced over 48 hours. Too-rapid correction of the fluid deficit or osmolality does not appear to increase the risk for the development of cerebral edema, a rare but devastating complication of DKA, which is more common in children.[59]

Potassium replacement is started as soon as the initial serum potassium is known, providing that it is less than 5.5 mEq/L and the patient is passing urine and not in acute renal failure.

Insulin :

For many years there has been debate about the optimal method and dose of insulin administration for patients with DKA or HHS. There is clear evidence that patients with DKA are insulin resistant and require supraphysiologic doses of insulin to ensure suppression of lipolysis and hepatic gluconeogenesis. Intravenously administered insulin has a half-life of 4 to 5 minutes, whereas regular insulin administered via the intramuscular or subcutaneous route has a half-life of –2 or 4 hours, respectively. After the discovery of insulin, patients with DKA were treated with small, frequent doses of intravenous or intramuscular insulin, but this soon gave way to “highdose” bolus insulin therapy. It was later realized that even “low” doses of insulin adminstered by intravenous infusion (doses of 4 to 8 units per hour) were sufficient to suppress lipolysis and hepatic gluconeogenesis by 100% and were associated with serum insulin levels of approximately 100μU/mL concentrations significantly higher than those in the average nondiabetic person. Large doses of insulin given intravenously intermittently every hour lead to much higher peak insulin levels that wane within approximately 30 mintues of the administration of insulin and result in minimal biologic effects for at least 15 minutes every hour. Thus, continuous infusion of “low-dose” insulin has become the standard of treatment in most medical centers. Such treatment is associated with fewer metabolic complications (i.e., hypoglycemia, hypokalemia, hypophosphatemia, hypomagnesemia, hyperlactatemia, and osmotic dysequilibrium) than is therapy with large, intermittent doses.

Intermittent low-dose intramuscular insulin (5 units) given every hour or every 2 hours after an initial intramuscular every hour or every 2 hours after an initial intramuscular loading dose of 20 units is also acceptable treatment for DKA, especially in centers where it is difficult to monitor low-dose intravenous infusions, and is associated with serum insulin levels of 60 to 90μU/mL With this treatment regimen, the initial decline in glucose is usually not as rapid as with intravenous insulin. Subcutaneous insulin can also be used in DKA, but because it takes longer to achieve peak insulin concentrations, it is associated with a less rapid initial decline in glucose concentrations and may cause late hypoglycemia more frequently than intramuscular insulin.

Guidelines for Insulin Management in Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State:

- Regular insulin 10 U i.v. stat (for adults) or 0.15 U/kg i.v. stat.
- Start regular insulin infusion 0.1 U/kg per hour or 5 U per hour.
- Increase insulin by 1 U per hour every 1-2 hr if less than 10% decrease in glucose or no improvement in acid-base status.
- Decrease insulin by 1-2 U per hour (0.5-0.1 U/kg per hour) when glucose ≤250 mg/dL and/or progressive improvement in clinical status with decrease in glucose of >75mg/dL per hour.
- Do not decrease insulin infusion to <1 U per hour.
- Maintain glucose between 140 and 180mg/dL.
- If blood sugar decreases to <80mg/dL, stop insulin infusion for no more than 1 hr and restart infusion.

- If glucose drops consistently to <100 mg/dL, change i.v. fluids to D10 to maintain blood glucose between 140 and 180mg/dL.
- Once patient is able to eat, consider change to s.c. insulin :

Overlap short-acting insulin s.c. and continue i.v. infusion for 1-2 hr.

For patients with previous insulin dose; return to prior dose of insulin.

For patients with newly diagnosed diabetes: full-dose s.c. insulin based on 0.6 U/kg per day.

Therefore, for the majority of patients, insulin is given simultaneously with intravenous fluids, starting with an intravenous loading dose of 0.15 U/kg body weight (usually 10 U in adults), followed by a continuous infusion of insulin at a rate of 0.1 U/kg per hour (usually 5 to 7 U per hour in adults). If the patient is in shock or the initial serum potassium level is less than 3.3 mEq/L, resuscitation with intravenous fluids or potassium replacement or both is instituted before commencing the insulin infusion. An insulin infusion of 5 to 7 U per hour should lower serum glucose concentrations by 50 to 75 mg/dL per hour and is usually sufficient to inhibit lipolysis, stop ketogenesis, and suppress hepatic gluconeogenesis.[60] The insulin infusion rate should be continually reassessed and increased if the rate of decrease in glucose is less than 50 mg/dL per hour, providing that other causes for the lack of response to therapy have been excluded. These include worsening of the acidosis and inadequate hydration. Once the serum glucose has decreased to less than 250mg/dL, the rate of infusion may often be decreased to 0.05 to 0.1U/kg per hour until the patient is able to take fluids and food by mouth. At this stage, a subcutaneous insulin regimen can be commenced, ensuring that the intravenous infusion is continued for at least 1 to 2 hours after the subcutaneous administration of short-acting insulin. Milder forms of DKA can be treated with subcutaneous or intramuscular insulin.

Comparison of intravenous subcutaneous, and intramuscular regimens for treatment of mild DKA has shown no significant difference in outcomes except for more rapid decrease in ketones and glucose during the first 2 hours of treatment with intravenous

insulin.[61]

Potassium :

Most patients with DKA and HHS have already lost considerable amounts of potassium at the time of presentation. Despite this, total body losses of serum potassium may be low, normal or elevated.[62] Intracellular dehydration and the metabolic acidosislead to intracellular depletion of potassium, which is largely an intracellular cation. Correction of the fluid deficit and acidosis in combination with insulin therapy leads to a shift of potassium back into the cells and a decrease in the serum potassium concentration. To prevent hypokalemia, potassium supplementation is started if the initial serum potassium is less than 5.5 mEq/L and urine output is adequate. Usually 20 to 30 mEq of potassium is added to each liter of fluid. Some authors prefer to use potassium chloride, and others use two thirds potassium chloride and one-third potassium phosphate. Larger concentrations of potassium are used if the serum potassium drops below 3.5 mEq/L. If the initial serum potassium is less than 3.3 mEq/L, potassium replacement is required before initiating the insulin infusion, which is started only when the potassium has risen to above 3.5 mEq/L.

Guideline for Potassium Replacement in Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

- Do not administer potassium if serum potassium >5.5 mEq/L or patient is anuric.

- Use KCI but alternate with KPO4 if there is severe phosphate depletion and patient is unable to take phosphate by mouth.

Serum K (mEq/L)	Additional K required
< 3.5	40 mEq/L
3.5 – 4.5	20 mEq/L
4.5 – 5.5	10 mEq/L
> 5.5	Stop K infusion

Bicarbonate :

The serum insulin concentrations achieved with the low-dose insulin infusion during treatment of DKA usually are sufficient to suppress lipolysis and reverseketogenesis. In most situations, treatment with insulin results in resolution of the acidbase abnormality. No studies to date have shown any benefit of bicarbonate therapy in patients with DKA whose pH between 6.9 and 7.1.[63] Severe acidosis, however, is associated with a number of adverse vascular effects, including hypotension, decreased cardiac output, decreased peripheral vascular resistance, increased pulmonary arterial resistance, braycardia, and arrhythmias. It also causes renal and mesenteric ischemia, cerebral vasodilatation, increased cerebrospinal fluid pressure, and coma; decreases the buffer reserve considerably; and also may increase insulin resistance[64] Potential adverse effects of bicarbonate therapy, on the other hand, include an overshoot alkalosis, paradoxical cerebrospinal fluid acidosis, hypokalemia, volume overload, alteration in tissue oxygenation, hypokalemia, volume overload, alteration in tissue oxygenation, and overproduction of ketoacids. Thus, treatment with bicarbonate should be considered only in patients whose pH is less than 7.0 unless some of the adverse clinical manifestations of acidemia are present. Usually 100 mL of sodium bicarbonate is mixed with 400 mL sterile water and administered

at a rate of 200 mL per hour intravenously. The venous pH should be checked 30 minutes later and treatment repeated if the pH remains below 7.0

Guidelines for Bicarbonate Therapy in Diabetic Ketoacidosis

- Use clinical judgement in deciding if bicarbonate therapy is indicated.
- If pH is <7.0, give 100 mL NaHCO3 over 45 min.
- Check acid-base status 30 min later and repeat if pH remains <7.0.

Phosphate :

Phosphate depletion is common in DKA and HHS. Intracellular phosphate is lost, and renal phosphate is lost, and renal phosphate excretion is increased. During treatment with insulin, phosphate is taken up intracellularly with resultant hypophosphatemia.[65]

Hypophosphatemia is associated with a number of clinical sequelae, including decreased cardiac output, respiratory muscle weakness, rhabdomyolysis, central nervous system depression, seizures and coma, acute renal failure, and hemolysis. Intravenous phosphate therapy may lead to hypocalcemia. Thus, the degree of phosphate replacement and type of phosphate treatment required in DKA remain controversial. Most studies have not shown any obvious benefit of routine phosphate replacement in DKA**.**[66] Phosphate replacement, therefore, should be reserved for those with severe hypophosphatemia of 1.5 mg/dL or less and in whom serum calcium concentrations are normal. The use of small amounts of potassium phosphate with potassium chloride given intravenously appears to be safe and effective. Oral phosphate repletion is always preferable to intravenous repletion and should be commenced as soon as patients are able to take food by mouth.

Ongoing Monitoring :

Successful management of DKA requires frequent clinical and laboratory reassessment. Blood glucose should be checked hourly (either fingerstick capillary blood glucose or venous plasma glucose), and electrolytes and acid-base status should be reviewed every 2 to 4 hours as indicated. Measurement of venous pH is acceptable for those in whom there is no need to assess arterial Po2 or Pco2. The venous pH is approximately 0.03 unit less than the arterial pH.[67]BUN and creatinine should be checked every 4 hours. Frequent measurement of serum or urine ketones is usually not necessary, providing that the patient is responding to treatment. During treatment of the acidosis, β-hydroxybutyrate is converted to acetoacetate, which may result in an apparent increase in the ketone concentration. Thus, frequent measurement of ketones (measuring acetoacetate) may be misleading. Bedside patient blood ketone testing that measures β-hydroxybutyrate has recently become available. Measurement of the rate of decline of β- hydroxybutyrate with this technique may facilitate treatment.[68] Use of a flow chart documenting clinical status (blood pressure, intake and output of fluids, and level of consciousness if indicated), serum glucose, electrolytes, and anion gap is recommended. If pneumonia is suspected and the initial chest radiograph shows no evidence of consolidation, a repeat chest radiograph should be performed after at least 4 L of fluid has been administered. Pregnancy testing should be considered for women of reproductive age because of the potential deleterious consequences of DKA and uncontrolled diabetes on fetal well-being.

Once the patient is able to tolerate oral fluids and start eating, the shift from intravenous to subcutaneous insulin should be undertaken. When changing to subcutaneous insulin, the intravenous infusion of insulin should be continued for 1 to 2 hours after the subcutaneous insulin has been administered, and the dextrose

infusion should be continued until the patient has eaten a meal. The initial dose of subcutaneous insulin should contain some short or rapid-acting insulin. Stopping the insulin infusion for more than 30 to 60 minutes without administering short or rapid-acting subcutaneous insulin should be avoided because the half-life of intravenous insulin is 2 to 4 minutes and ketoacidosis may recur rapidly in the absence of exogenous insulin.

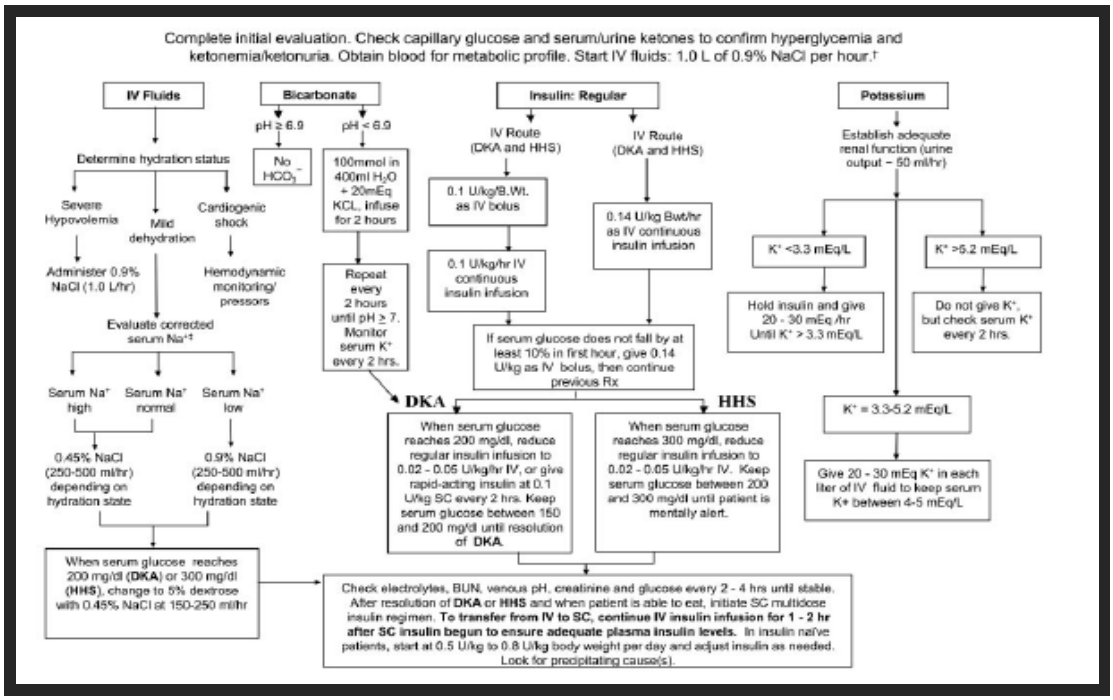

Fig 10. Protocol for management of adult patients with DKA or HHS. DKA diagnostic criteria: blood glucose 250 mg/dl, arterial pH 7.3, bicarbonate 15 mEq/l, and moderate ketonuria or ketonemia. HHS diagnostic criteria: serum glucose 600 mg/dl, arterial pH _7.3, serum bicarbonate _15 mEq/l, and minimal ketonuria and ketonemia. †15–20 ml/kg/h; ‡serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose 100 mg/dl, add 1.6 mEq to sodium value for corrected serum value). (Adapted from ref. 69) Bwt, body weight; IV, intravenous; SC, subcutaneous.

Complications of Therapy :

Hypoglycemia and hypokalemia remain common complications of therapy. Both can be avoided by ensuring appropriate glucose and potassium administration as recommended earlier in the chapter. Hypophosphatemia may occur during therapy. There are no data supporting the use of intravenous potassium phosphate routinely during treatment of DKA. Intravenous phosphate should be given judiciously, but oral phosphate repletion should commence as soon as the patient is able to tolerate food and fluids by mouth. Persistent acidosis that does not respond to therapy may be caused by hypophosphatemia, sepsis, and inadequate insulin administration.

Hyperchloremia and hyperchloremic acidosis may occur during treatment of DKA. Because replacement solutions have equal parts of sodium and chloride, relative hyperchloremia will occur during treatment. This is usually of no clinical consequence, and normalization of the anion gap during treatment with persistent reduction of bicarbonate is not an unexpected finding during the course of treatment.

Hypocalcemia may occur during treatment, especially during therapy with phosphate. Serum calcium levels should be checked before phosphate supplementation is started.

Pulmonary edema or respiratory distress syndrome or both may occur during treatment of DKA and HHS. Elderly patients are at risk for this complication, which may be caused by excessive fluid replacement left ventricular dysfunction, or a capillary leak syndrome. Ongoing assessment of oxygen saturation and fluid balance, sometimes with invasive hemodynamic monitoring, is critical during treatment.

Cerebral edema is a rare complication of treatment of DKA. Clinically significant cerebral edema is more likely to occur in children, affecting approximately 1% of all children with DKA, but it is very rare in adults.[70] Children at risk for the development of cerebral edema include those with lower Pco2 and high BUN concentrations at

presentation, those whose serum sodium level rises more slowly during therapy, and those who require bicarbonate therapy. The rate of fluid administration and rate of decline of glucose concentrations do not appear to be associated with the development of cerebral edema in children.[59]Sudden deterioration of level of consciousness in a child being treated for DKA should arouse clinical suspicious for cerebral edema.

Hyperosmolar therapy remains the treatmer of choice for these situations. Venous thrombosis and pulmonary embolism are rare "complication" of DKA and HHS.[70] Patients presenting with dehydration and electrolyte imbalance are in ahypercoagulable state. Prophylaxis for venous thromboembolism should be considered in those most at risk, including the elderly and obese patients

Prevention :

DKA is a preventable disorder. Infection and inadequate insulin administration (inappropriate reduction of omission of insulin and noncompliance with insulin regimens remain the most common causes of DKA. Patient education and 24 hour access to advice and care remains the cornerstone of preventative therapy. Patients should be taught how to manage their diabetes during periods of stress or inter current infection ("sick-day" rules) and should understand the importance of frequent monitoring of blood glucose concentrations, urine ketones, temperature, and, if necessary, blood pressure, pulse, and weight during these time. They should have access to healthcare providers who are trained to manage diabetes during these periods and who are familiar with guidelines for referral to an emergency department, should home management be unsuccessful or should vomiting develop. Education programs have been shown to reduce the rate of episodes and admissions for DKA in susceptible group of patients. The elderly patient living in a nursing home, who is unable to keep up with fluid losses or is unaware of fluid losses during intercurrent

illness, is particularly at risk for the development HHS. Education of caregivers who should learn to recognize signs and symptoms of increasing hyperglycemia will reduce the incidence of severe HHS. These people should also know where to increase the frequency of blood glucose monitoring in those at risk and should have access to specialty care if indicated.

COMPLICATIONS OF DIABETIC KETOACIDOSIS :

Cerebral Oedema

Cerebral oedema is an imperfectly understood complication of diabetic ketoacidosis and its treatment, which remains an important cause of mortality in thesepatients. Children appear to be particularly at risk. Clinically apparent cerebral oedema develops in 1-2% of ketoacidotic diabetic children , although subclinical oedema demonstrable by computed tomography (CT) scanning or raised cerebrospinal fluid (CSF) pressure probably occurs in most cases during treatment and indeed is likely to be present even before treatment begins . The mortality in established cerebral oedema exceeds 90%, and the condition is a major cause of death in newly presenting cases of ketoacidosis, accounting for 50% of fatalities . Ultimately, cerebral oedema is due to excessive entry of water into cells of the brain, causing it to swell. This cannot be accommodated within the enclosed space of the cranium, and the base of the brain is forcibly herniated through the foramen magnum.

The cerebellar tonsils impact in the opening and are pushed inwards to compress the medulla, which contains the respiratory centres. This ‘coning’ causes a progressive and often rapid fall in conscious level, terminating inrespiratory arrest

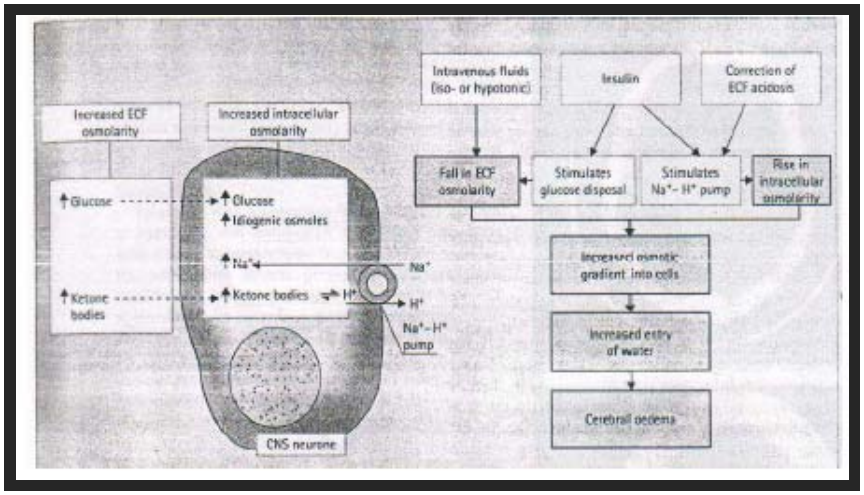

Fig. 11. Hypothetical mechanisms involved in the pathogenesis of cerebral oedema in patients with diabetic ketoacidosis.

The cellular mechanisms responsible remain uncertain. These need to be able to explain why mild cerebral oedema occurs commonly at presentation of diabeticketoacidosis (but not, apparently, in hyperosmolar non-ketotic states), and why it may worsen some hours after starting treatment with intravenous fluids and insulin. During the period of extracellular-fluid (ECF) hyperosmolarity that accompanies the dehydration of untreated ketoacidosis, the brain must accumulate intracellular osmotically active molecules in order to prevent cellular shrinkage. Animal studies suggest that these include glucose and unidentified molecules (collectively termed 'idiogenic osmoles'), which are produced within the brain cells and which may account for one-half of the additional osmotic load. Ketone bodies have also been suggested to enter brain cells, where they may generate hydrogen ions; it has been suggested that these are then extruded from the cells by the Na+-H+ membrane pump in exchange for sodium ions that enter the cells. By enhancing intracellular sodium accumulation, this would further favour entry of water into the brain. Theoretically, this could explain why raised ketonebody levels are essential for

the development of cerebral oedema, although the extent to which ketone bodies enter the brain is controversial.

Treatment with intravenous fluids, whether isotonic or hypotonic, will temporarily reduce ECF osmolarity with respect to intracellular fluid (ICF) brain osmolarity, with which it was previously in approximate equilibrium. Insulin treatment will also reduce ECF hyperosmolarity by reducing circulating glucose concentrations, and it is also thought to stimulate the Na+-H+ exchanger, which would promote further sodium entry into brain cells . However, there is little clinical evidence to implicate insulin treatment in the pathogenesis of cerebral oedema . The Na+-H+ exchanger may also be stimulated by a fall in extracellular hydrogen ions and by any rise in intracellular acidosis that may result from bicarbonate treatment. As mentioned above, the use of bicarbonate was an independent predictor of the development of cerebral oedema in a recent prospective study of 61 children with moderately severe diabetic ketoacidosis. The speed with which these adverse changes occur may be critical, by not allowing the brain cells to expel osmotically active molecules. Animal experiments have suggested that rapid reductions of plasma glucose concentration to below 14 mmol/L may be important in causing cerebral oedema , although there is little support for this view in published case reports. The use of hypotonic fluids during treatment has also been implicated, but the evidence remains inconclusive. A common factor in two-thirds of cases in one series was a recent fall in plasma sodium concentration that exceeded 4 mmol/L; excessively rapid correction of plasma hyperosmolality could cause free water to enter the brain, whose intracellular osmolality would remain relatively high.

Cerebral oedema presents clinically as a decline in conscious level, often progressing rapidly to coma and culminating within a few hours in cardiorespiratory

arrest. Typically, the process begins within 8-24 h after starting intravenous fluid and insulin treatment, and many patients deteriorate without warning, having appeared until then to have responded well to therapy. Very few patients with clinical evidence of raised intracranial pressure or cerebral herniation will recover. The diagnosis should be confirmed by CT or magnetic resonance (MR) scanning of the brain, which shows swelling of the brain, with loss of structural detail and squashing of the ventricular system. Imaging must always be performed in patients whose conscious level decreases, because other cerebral events such as stroke may have occurred and may have a more favourable prognosis. CSF pressure is raised, and this may be used to monitor progress.

The gloomy prognosis of cerebral oedema may partly be due to delays in diagnosing and treating the condition. No adequate clinical trials have been performed, but reasonable measures would include:

- Slowing the rate of intravenous fluid infusion and avoiding hypotonic fluids.
- Decreasing the rate of insulin delivery.
- Giving intravenous mannitol to raise ECF osmolarity.

Suggested mannitol dosages range from 0.2g/kg (given over 30 min, initially and repeated hourly if there is no improvement) to single doses of 1 g/kg. Dexamethasone is often given in high dosages (e.g. 4mg 6-hourly intravenously), but its benefits remain unproven. Mechanical ventilation to remove carbon dioxide and improve acidosis has also been advocated.

Adult respiratory distress syndrome:

Adult respiratory distress syndrome has been reported occasionally in patients with ketoacidosis, usually in patients under 50years of age. Clinical features include dyspnoea, trachypnoea, central cyanosis and non-specific chest signs. Arterial

hypoxia is characteristic, and chest radiography reveals bilateral pulmonary infiltrates that resemble pulmonary oedema. Management involves respiratory support with intermittent positivepressure ventilation and avoidance of fluid overload.

Thromboembolism :

Thromboembolism complications are important causes of mortality in patients with diabetic ketoacidosis, arising from dehydration, increased blood viscosity and increased coagulability. Disseminated intravascular coagulation has also been reported as a rare complication of diabetic ketoacidosis. The role of prophylactic anticoagulation has not been clearly established in diabetic ketoacidosis, and routine anticoagulation is not recommended in view of the risks of bleeding. Established thromboembolic complications are treated conventionally.

Rhinocerebral Mucormycosis :

Rarely, an aggressive opportunistic fungal infections develop in diabetic patients, who often present with diabetic ketoacidosis or other metabolic acidosis . The lesion arises in the paranasal sinuses and rapidly invades adjacent tissues (nose, sinuses, orbitand brain). Treatment comprises correction of acidosis, surgical excision of affected tissue condition and parenteral antifungal agents. The course is often fulminant, and the condition carries a high mortality.

Microvascular and Macrovascular Complications of Diabetes

Diabetic retinopathy

The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia. Development of diabetic retinopathy in patients with type 2 diabetes was found to be related to both severity of hyperglycemia and presence of hypertension in the U.K. Prospective Diabetes Study (UKPDS), and most patients

with type 1 diabetes develop evidence of retinopathy within 20 years of diagnosis.[71] Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes.[72]

Aldose reductase may participate in the development of diabetes complications. Aldose reductase is the initial enzyme in the intracellular polyol pathway. This pathway involves the conversion of glucose into glucose alcohol (sorbitol). High glucose levels increase the flux of sugar molecules through the polyol pathway, which causes sorbitol accumulation in cells. Osmotic stress from sorbitol accumulation has been postulated as an underlying mechanism in the development of diabetic microvascular complications, including diabetic retinopathy. Treatment studies with aldose reductase inhibitors, however, have been disappointing.[72,73] Cells are also thought to be injured by glycoproteins. High glucose concentrations can promote the nonenzymatic formation of advanced glycosylated end products (AGEs). Evaluations of AGE inhibitors are underway Growth factors, including vascular endothelial growth factor (VEGF), growth hormone, and transforming growth factor β, have also been postulated to play important roles in the development of diabetic retinopathy. VEGF production is increased in diabetic retinopathy, possibly in response to hypoxia.

Diabetic retinopathy is generally classified as either background or proliferative.

Background retinopathy includes such features as small hemorrhages in the middle layers of the retina. They clinically appear as “dots” and therefore are frequently referred to as “dot hemorrhages.” Hard exudates are caused by lipid deposition that typically occurs at the margins of hemorrhages. Microaneurysms are small vascular dilatations that occur in the retina, often as the first sign of retinopathy.

They clinically appear as red dots during retinal examination. Retinal edema may result from microvascular leakage and is indicative of compromise of the blood-retinal barrier.

The appearance is one of grayish retinal areas. Retinal edema may require intervention because it is sometimes associated with visual deterioration.[74] Proliferative retinopathy is characterized by the formation of new blood vessels on the surface of the retina and can lead to vitreous hemorrhage. White areas on the retina ("cotton wool spots") can be a sign of impending proliferative retinopathy. If proliferation continues, blindness can occur through vitreous hemorrhage and traction retinal detachment. With no intervention, visual loss may occur. Laser photocoagulation can often prevent proliferative retinopathy from progressing to blindness; therefore, close surveillance for the existence or progression of retinopathy in patients with diabetes is crucial.[74]

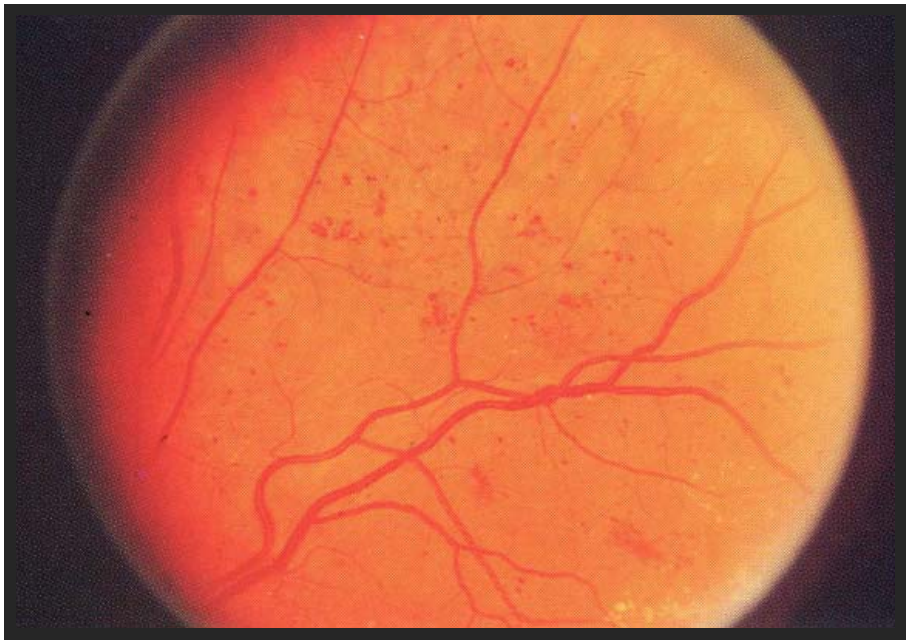

FIG 12. Back ground diabetic retinopathy showing scattered Red Dots and Blots (micro aneurysm ,haemorrages) and exudates

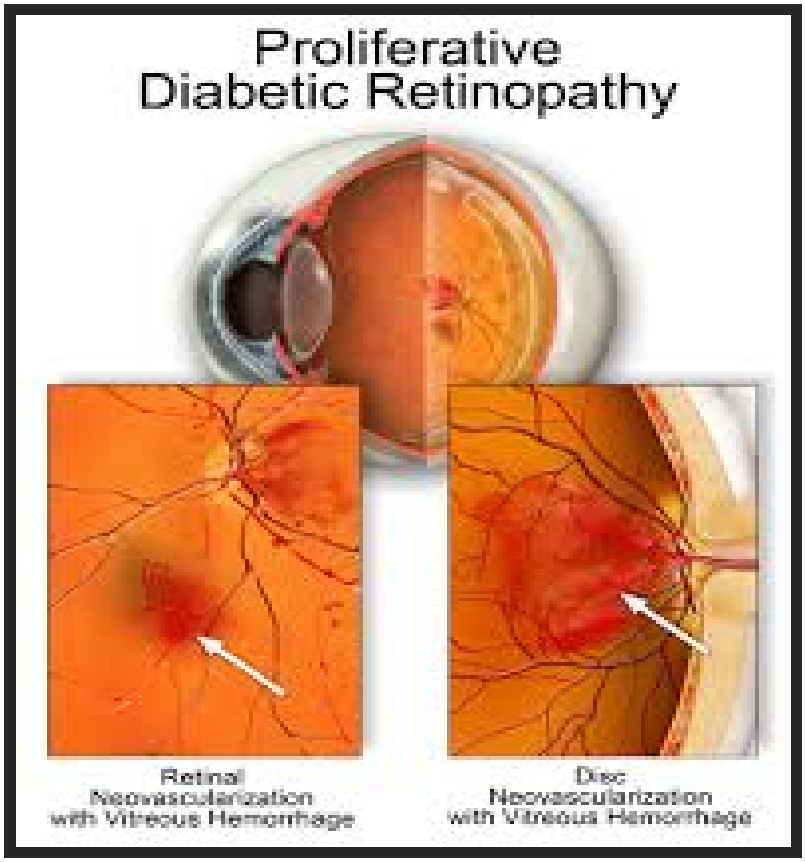

Fig : 13 Diabetic nephropathy

It is defined by proteinuria > 500mg in 24 hours in the setting of diabetes, but this is preceded by lower degrees of proteinuria, or "microalbuminuria." Microalbuminuria is defined as albumin excretion of 30–299 mg/24 hours. Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy. This progression occurs in both type 1 and type 2 diabetes. The pathological changes to the kidney include increased glomerular basement membrane thickness, microaneurysm formation, mesangial nodule formation (Kimmelsteil-Wilson bodies), and other changes. The underlying mechanism of injury may also involve some or all of the same mechanisms as diabetic retinopathy.Screening for diabetic nephropathy or microalbuminuria may be accomplished by either a 24-hour urine collection or a spot urine measurement of

microalbumin. Measurement of the microalbumin-to-creatinine ratio may help account for concentration or dilution of urine, and spot measurements are more convenient for patients than 24-hour urine collections. Like other microvascular complications of diabetes, there are strong associations between glucose control (as measured by haemoglobin A1c [A1C]) and the risk of developing diabetic nephropathy. Patients should be treated to the lowest safe glucose level that can be obtained to prevent or control diabetic nephropathy.[75] Treatment with angiotensin-converting enzyme (ACE) inhibitors has not been shown to prevent the development of microalbuminuria in patients with type 1 diabetes but has been shown to decrease the risk of developing nephropathy and cardiovascular events in patients with type 2 diabetes.[75] In addition to aggressive treatment of elevated blood glucose, patients with diabetic nephropathy benefit from treatment with antihypertensive drugs. Renin-angiotensin system blockade has additional benefits beyond the simple blood pressure–lowering effect in patients with diabetic nephropathy.Several studies have demonstrated renoprotective effects of treatment with ACE inhibitors and antiotensin receptor blockers (ARBs), which appear to be present independent of their blood pressure– lowering effects, possibly because of decreasing intraglomerular pressure.

Diabetic neuropathy

Diabetic neuropathy is recognized by the American Diabetes Association (ADA) as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes."[76] As with other microvascular complications, risk of developing diabetic neuropathy is proportional to both the magnitude and duration of hyperglycemia, and some individuals may possess genetic attributes that affect their predisposition to developing such complications The precise nature of injury to the peripheral nerves from hyperglycemia is not known but

likely is related to mechanisms such as polyol accumulation, injury from AGEs, and oxidative stress. Peripheral neuropathy in diabetes may manifest in several different forms, including sensory, focal/multifocal, and autonomic neuropathies. More than 80% of amputations occur after foot ulceration or injury, which can result from diabetic neuropathy.[77]

Chronic sensorimotor distal symmetric polyneuropathy is the most common form of neuropathy in diabetes. Typically, patients experience burning, tingling, and "electrical" pain, but sometimes they may experience simple numbness. In patients who experience pain, it may be worse at night Physical examination reveals sensory loss to light touch, vibration, and temperature. Abnormalities in more than one test of peripheral sensation are > 87% sensitive in detecting the presence of neuropathy. Patients also typically experience loss of ankle reflex.[77]

Pure sensory neuropathy is relatively rare and associated with periods of poor glycemic control or considerable fluctuation in diabetes control. It is characterized by isolated sensory findings without signs of motor neuropathy. Symptoms are typically most prominent at night.[77]

Mononeuropathies typically have a more sudden onset and involve virtually any nerve, but most commonly the median, ulnar, and radial nerves are affected. Cranial neuropathies have been described but are rare. It should be noted that nerve entrapment occurs frequently in the setting of diabetes. Electrophysiological evaluation in diabetic neuropathy demonstrates decreases in both amplitude of nerve impulse and conduction but may be useful in identifying the location of nerve entrapment.

Diabetic amyotrophy may be a manifestation of diabetic mononeuropathy and is characterized by severe pain and muscle weakness and atrophy, usually in large thigh muscles.[77]

Diabetic autonomic neuropathy also causes significant morbidity and even mortality in patients with diabetes.

Neurological dysfunction may occur in most organ systems and can by manifest by gastroparesis, constipation, diarrhea, anhidrosis, bladder dysfunction, erectile dysfunction, exercise intolerance, resting tachycardia, silent ischemia, and even sudden cardiac death.[77] Cardiovascular autonomic dysfunction is associated with increased risk of silent myocardial ischemia and mortality. There is no specific treatment of diabetic neuropathy. Some studies have suggested that control of hyperglycemia andavoidance of glycemic excursions may improve symptoms of peripheral neuropathy. Amitriptyline, imiprimine, paroxetine, citalopram, gabapentin, pregablin, carbamazepine, topiramate, duloxetine, tramadol, and oxycodone have all been used to treat painful symptoms, but only duloxetine and pregablin possess officialindications for the treatment of painful peripheral diabetic neuropathy.

Macrovascular Complications of Diabetes

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body.

Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from LDL particles accumulate in the endothelial wall of arteries. Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into

macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce smooth muscle proliferation in the arterial walls and collagen accumulation.The net result of the process is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction.[78]

In addition to atheroma formation, there is strong evidence of increased platelet adhesion and hypercoagulability in type 2 diabetes. Impaired nitric oxide generation and increased free radical formation in platelets, as well as altered calcium regulation, may promote platelet aggregation. Elevated levels of plasminogen activator inhibitor type 1 may also impair fibrinolysis in patients with diabetes. The combination of increased coagulability and impaired fibrinolysis likely further increases the risk of vascular occlusion and cardiovascular events in type 2 diabetes**.** Diabetes increases the risk that an individual will develop cardiovascular disease (CVD). Although the precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined, the association between the two is profound. CVD is the primary cause of death in people with either type 1 or type 2 diabetes.[79] Type 2 diabetes typically occurs in the setting of the metabolic syndrome, which also includes abdominal obesity, hypertension, hyperlipidemia, and increased coagulability. These other factors can also act to promote CVD.

Patients with type 2 diabetes have a much higher risk of stroke, with an increased risk of 150–400%. Studies in type 1 diabetes have shown that intensive diabetes control is associated with a lower resting heart rate and that patients with higher degrees of hyperglycemia tend to have a higher heart rate, which is associated

with higher risk of CVD.[79] Even more conclusively, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study demonstrated that during 17 years of prospective analysis, intensive treatment of type 1 diabetes, including lower A1C, is associated with a 42% risk reduction in all cardiovascular events and a 57% reduction in the risk of nonfatal MI, stroke, or death from CVD. There has not been a large, longterm, controlled study showing decreases in macrovascular disease event rates from improved glycemic control in type 2 diabetes.

Blockade of the reninangiotensin system using either an ACE inhibitor or an ARB reduced cardiovascular endpoints more than other antihypertensive agents. Another target of therapy is blood lipid concentration. Numerous studies have shown decreased risk in macrovascular disease in patients with diabetes who are treated with lipid-lowering agents, especially statins. In addition to statin therapy, fibric acid derivates have beneficial effects. They raise HDL levels and lower triglyceride concentrations and have been shown to decrease the risk of MI in patients with diabetes in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.20,26,35–39©.

MATERIALS AND METHODS

This study consists of 50 Patients of Diabetes mellitus with Hyperglycemic emergencies admitted to R.L.Jalappa hospital attached to Sri Devraj URS Medical College, between January 2013 to December 2013 were studied.

The following patients were included in the study:-

1. Diabetes mellitus type 1 and 2 presenting with Random blood sugar >250 mg/dl ,with either of the following-
    - Presence of ketone bodies in the blood or urine ketone bodies and metabolic acidosis(pH <7.30 or HCO3 <15 meq/L).
    - Dehydration and serum osmolality >300mOsm/kg.
2. Patients of age above 18 years.

All consecutive patients presenting to R.L.Jalappa hospital emergency with above inclusion criteria fulfilled will be included in this study after taking informed written consent. Presenting complaints, examination findings, investigations will be noted and patients will be followed up from the time of admission till discharge/death. The data was collected and recorded in the proforma.

Following investigations were carried out:

1. Hematological and biochemical investigations:
    a. Hb%, WBC count total and differential.
    b. Blood sugar estimation was done by folin Wu method.
    c. Serum electrolytes by flame photometry.

Normal values:

Serum sodium 136-145 mEq/L

Serum potassium 3.6 – 5.5 mEq/L

d. Blood urea estimation

Urea Nesselerization method

Normal 25-40 mg/dl

e. Serum creatinine

Normal value: 0.5 – 1.9 mg/dl

Radiological Investigation:

X-ray chest: PA view to see lung pathology

E.C.G.: To see evidence of ischaemic heart disease and K+ changes in serial ECG's

Urine: For routine and microscopy

Urine culture and sensitivity

Urine Sugar:

Benedict's Qualitative Test:

If the original blue colour of reagent changes to green/yellow-orange/ brick red..

Urine Albumin:

By heat and acetic acid test; results are interpreted as 1 + to 4+.

Urine for Ketone Bodies:

Rothera's Test for acetone and acetoacetic acid:-

A volume of 10 ml urine is saturated with an excess of ammonium sulfate crystals. 3 drops of a strongly freshly prepared solution of sodium nitroprusside and 2 ml of strong ammonia solution are then added. A deep permanganate colour is produced by acetone and acetoacetic acid. If Rothera's test is negative, ketones are absent.

Presence of ketone bodies in urine is suggestive of diabetic ketoacidosis. In diabetic ketoacidosis serial urine sugar and acetone estimation were done and gave idea regarding the course of the disease and outcome of therapy.

- Fundoscopy : For Diabetic Retinal chnges
- 2D Echocardiograph: For CADs
- CT Scan Brain Plain: For CVA

Statistical analysis:

Data was entered into Microsoft excel and analyzed using EPI info 7 version software. Data was represented in the form of Frequencies and Percentages. Bar diagrams and Pie charts were used for graphical representation of the data. Chi-square test was the test of significance for qualitative data and t test was the test of significance for Quantitative data. p value <0.05 was considered statistically significant.

RESULTS

Table 1: Age distribution of Subjects with Hyperglycemic emergency in Diabetes

		Emergency				
		DKA		HHS		
		No.	Row %	No.	Row %	Total
Age	<30 yrs	7	87.5%	1	12.5%	8
	31 to 40 yrs	5	71.4%	2	28.6%	7
	41 to 50 yrs	3	60.0%	2	40.0%	5
	51 to 60 yrs	5	38.5%	8	61.5%	13
	>60 yrs	2	11.8%	15	88.2%	17
Total		22	44.0%	28	56.0%	50

$\chi 2 = 16.13$, df=4, p =0.003**

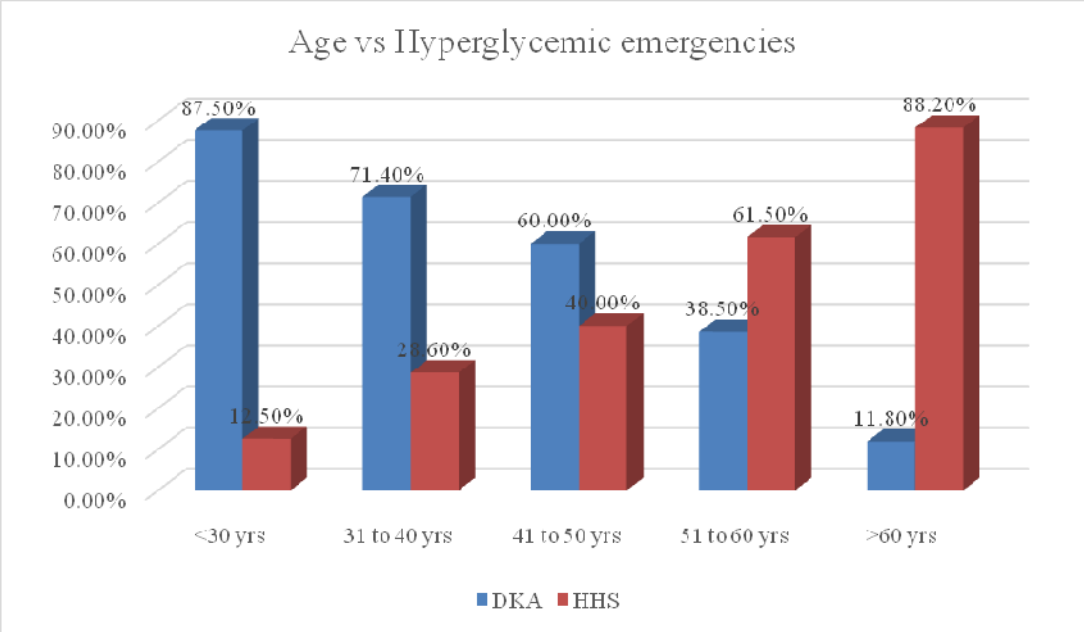

Figure 1: Bar diagram showing association between age and hyperglycemic emergencies

In the study total of 50 subjects of diabetes with hyperglycemic emergencies were included. Of which 22 (44%) subjects had Diabetic Ketoacidosis (DKA) and 28 (56%) patients had HHS (Hyperglycemic Hyperosmolar Non Ketotic state).

Among <30 yrs age group 7 (87.5%) had DKA and 1 (12.5%) had HHS, Similarly in 31 to 40 yrs age group 5 (71.4%) had DKA and 2 (28.6%) had HHS. Among 41 to 50 yrs age group DKA was seen in 3 (60%) and 2 (40%) had HHS. Where as after 50 yrs HHS was common than DKA i.e. in the age group 51 to 60 yrs 8 (61.5%) had HHS and 5 (38.5%) had DKA and in the age group >60 yrs 15 (88.2%) had HHS and DKA in 2 (11.8%). Hence in younger age group DKA was common and after 50 yrs HHS was common. This observation was statistically significant.

Table 2: Sex distribution of Subjects with Hyperglycemic emergency in Diabetes

		Emergency				Total
		DKA		HHS		
		No	Row %	No	Row %	
Gender	Female	12	66.7%	6	33.3%	18
	Male	10	31.2%	22	68.8%	32
Total		22	44.0%	28	56.0%	50

$\chi 2 = 5.86$, df=1, p =0.015**

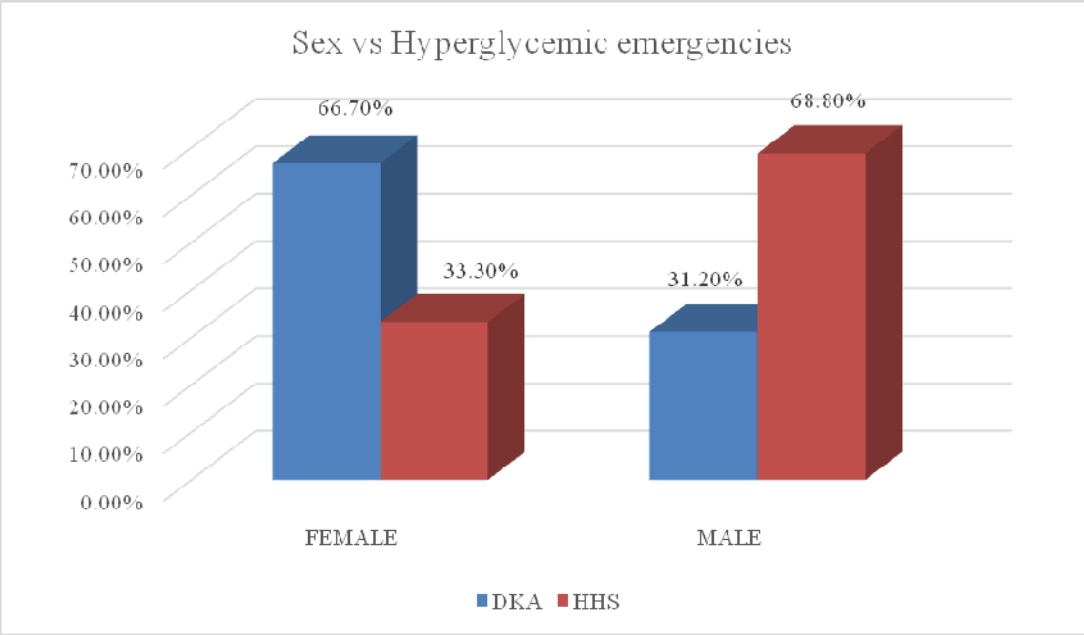

Figure 2: Bar diagram showing association between sex and Hyperglycemic emergencies

In the study 18(36%) were females and 32 (64%) were males. Among 18 females 12 (66.7%) had DKA and 6 (33.3%) had HHS. Among 32 males 22 (68.8%) had HHS and 10 (31.2%) had DKA. Hence it can be said that DKA was common among females and HHS in males. This observation was statistically significant.

Table 3: Type of diabetes among subjects with Hyperglycemic emergency in Diabetes

		Emergency				Total
		DKA		HHS		
		No	%	No	%	
Type of DM	**1**	12	80.0%	3	20.0%	15
	2	10	28.6%	25	71.4%	35
Total		22	44.0%	28	56.0%	50

$\chi 2 = 11.27$, df=1, p =0.001**

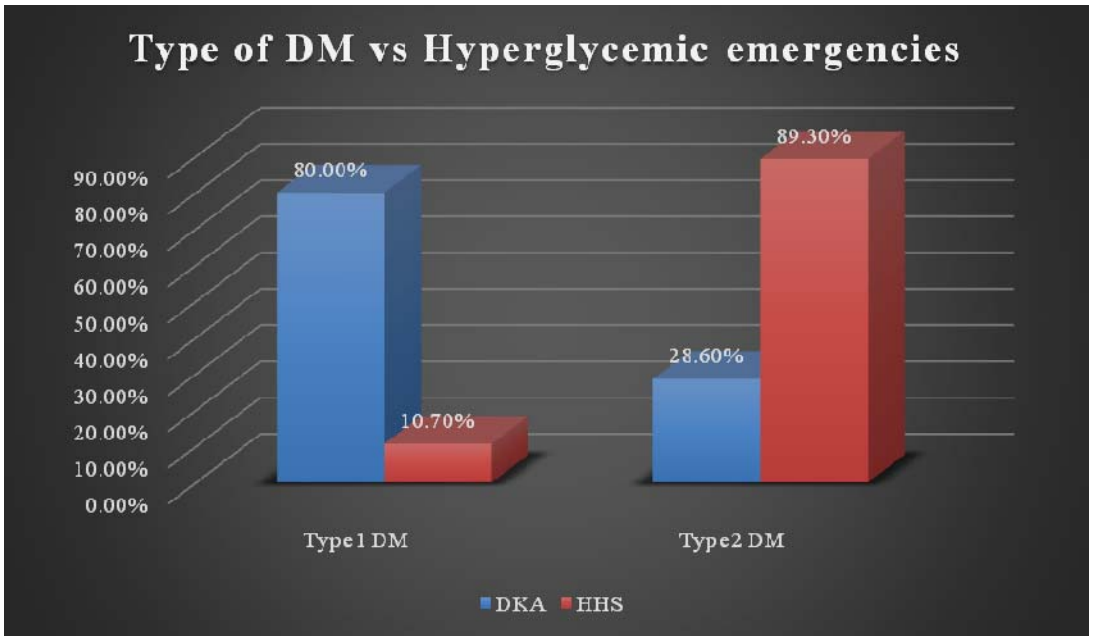

Figure 3: Bar diagram showing association between Type of DM and Hyperglycemic emergencies

It was observed that among 50 patients, 30% had Type 1 DM and 70% had Type 2 DM. Among 15 type 1 DM subjects 12 (80%) had DKA and 3 (20%) had HHS. Among 35 Type 2 DM subjects 71.4% had HHS and 28.6% had DKA. From this it can be said that DKA is common in Type 1 DM and HHS in Type 2 DM. This association was statistically significant.

Table 4: Clinical features among subjects with Hyperglycemic emergency in Diabetes

	Emergency				**Total**		**p value**
	DKA (n=22)		**HHS (n=28)**				
	No	%	No	%	No	%	
Vomiting	9	34.6%	17	65.4%	26	52%	0.164
Nausea	5	35.7%	9	64.3%	14	28%	0.462
Dehydration	1	33.3%	2	66.7%	3	6.0%	0.701
Altered sensorium	3	42.9%	4	57.1%	7	14.0%	0.948
Abdominal Pain	2	28.6%	5	71.4%	7	14.0%	0.375
Tachycardia	1	25.0%	3	75.0%	4	8.0%	0.425
Acidotic breathing	8	88.9%	1	11.1%	9	18.0%	0.003**

It was observed that out of 50 subjects, 26 (52%) had vomiting, 14 (28%) had Nausea, 3 (6%) had dehydration, 7 (14%) had altered sensorium and abdominal pain, 4 (8%) had Tachycardia and 9 (18%) had Acidotic breathing.

Among those who had vomiting 17 (65.4%) had HHS and 9 (34.6%) had DKA.

Among those who had Nausea 9 (64.3%) had HHS and 5 (35.7%) had DKA.

Similarly majority of the features were common among HHS subjects except Acidotic breathing which was seen in 8 out of 9 (88.9%) subjects. This observation of acidotic breathing being high among DKA subjects was statistically significant.

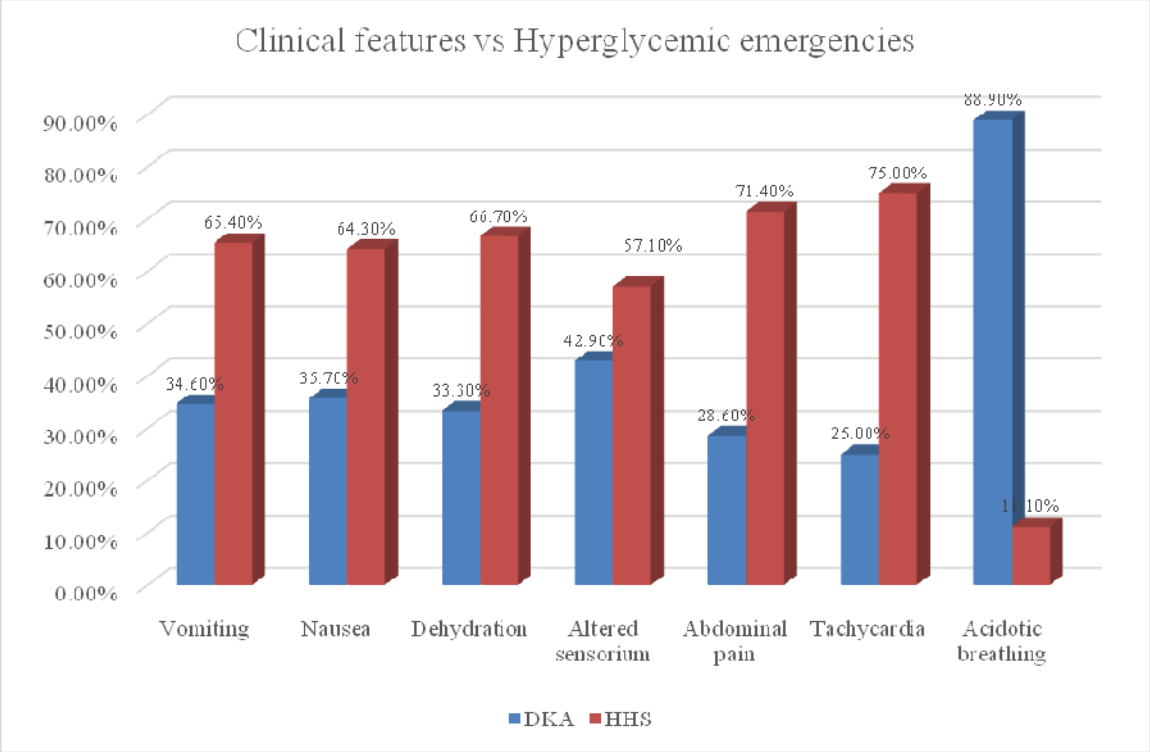

Figure 4: Bar diagram showing association between clinical features and hyperglycemic emergencies

Table 5: Factors associated with Hyperglycemic emergency in Diabetes

	DKA (n=22)		HHS (n=28)		p value
	Mean	**SD**	**Mean**	**SD**	
Age (Yrs)	41.95	15.77	62.93	14.45	<0.001**
Duration of diabetes(yrs)	8.86	4.87	15.18	6.09	<0.001**
RBS at admission (mg/dl)	454.45	61.75	600	0.00	<0.001**
HbA1c %	11.47	1.21	12.21	1.14	.032
Blood urea(mg/dl)	37.86	12.9	41.82	13.42	.299
Serum Creatinine(mg/dl)	0.773	0.23	0.843	0.28	.361
Na+(meq/l)	131.64	7.65	133.89	11.97	.446
K+(meq/l)	3.823	1.25	3.99	1.19	.627
PH	7.13	0.03	7.39	0.06	<0.001**
Serum osmolality (mosm/kg)	312.68	3.65	347.46	5.18	<0.001**
Insulin Requirement (units)	58.18	12.05	103.54	21.19	<0.001**

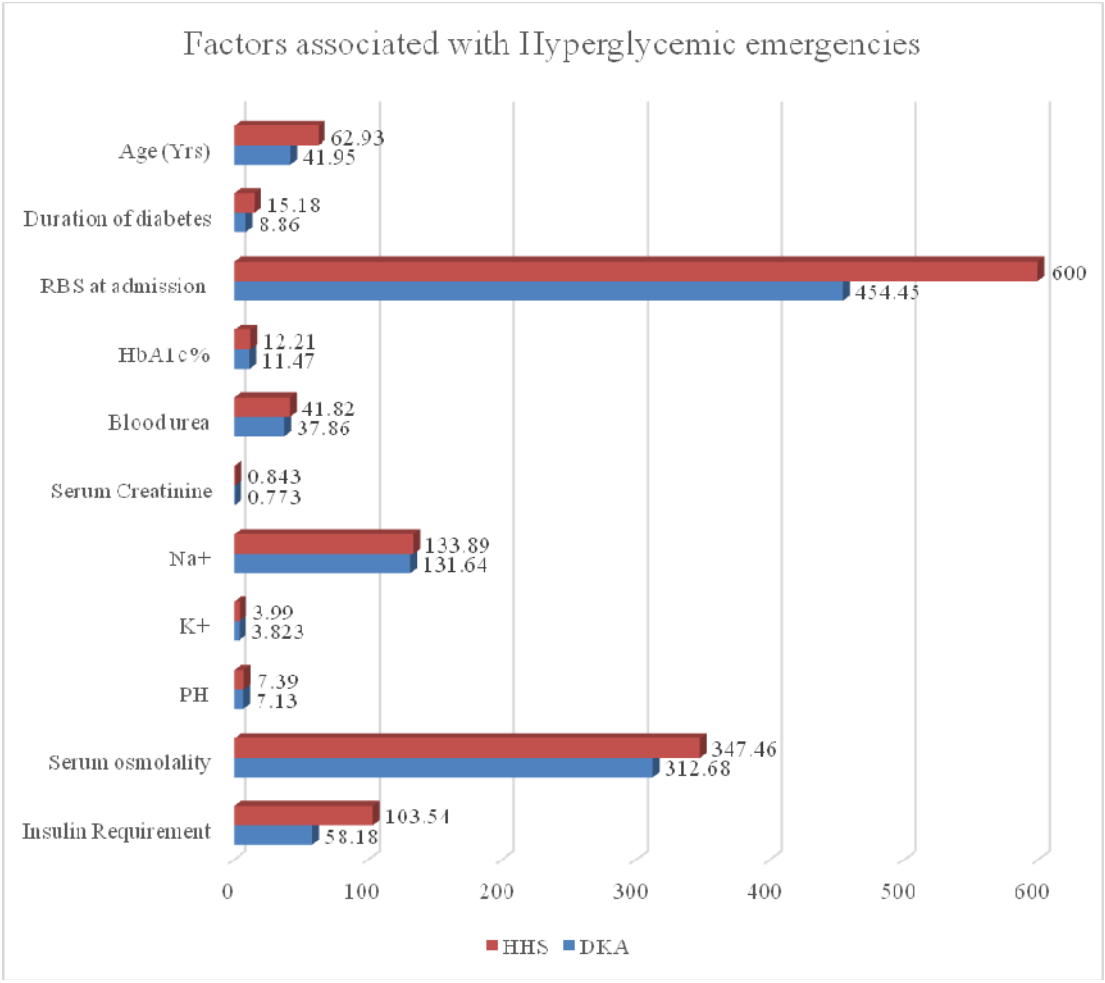

Figure 5: Bar diagram showing factors associated with Hyperglycemic emergencies

In the study significant association was observed in age, Duration of diabetes, RBS at admission, PH, Serum Osmolality and Insulin requirement.

Mean age for DKA was less when compared to HHS. DKA was common in Younger individuals and HHS was seen among elderly individuals.

Mean duration of diabetes was high among HHS than DKA group. I.e. more the duration of diabetes more the risk for HHS, since type 1 DM is common among

younger individuals mean duration of diabetes among DKA was lower than HHS group.

RBS average value in DKA group was 454 mg/dl and in HHS group was 600 mg/dl. This difference was statistically significant. I.e. in HHS group RBS will be more than DKA patients.

Mean PH was lower among DKA subjects than HHS group because of acidosis. This difference was statistically significant.

Mean Serum osmolality was lower among DKA subjects than HHS. This difference was statistically significant.

Mean Insulin requirement was less in DKA subjects than HHS group. This difference was statistically significant.

Table 6: Infectious Precipitating Factors associated with Hyperglycemic emergency in Diabetes

Precipitating factors	**Emergency**				**Total**	
	DKA		**HHS**			
	No	%	No	%	No	Column%
Diabetic foot	7	46.7%	8	53.3%	15	30.0%
Perianal abscess	0	-	1	100.0%	1	2.0%
Pneumonia	9	56.2%	7	43.8%	16	32.0%
Sepsis	2	20.0%	8	80.0%	10	20.0%
Urinary tract infection	4	50.0%	4	50.0%	8	16.0%

Precipitating factors	Emergency				Total	
	DKA		HHS			
	No	%	No	%	No	Column%
Diabetic foot	7	46.7%	8	53.3%	15	30.0%
Perianal abscess	0	-	1	100.0%	1	2.0%
Pneumonia	9	56.2%	7	43.8%	16	32.0%
Sepsis	2	20.0%	8	80.0%	10	20.0%
Urinary tract infection	4	50.0%	4	50.0%	8	16.0%
Total	22	44.0%	28	56.0%	50	100%

$\chi 2 = 4.25$, df=4, p =0.372

In the study among 50 subjects15 (30%) had Diabetic Foot, 1 (2%) had Perianal abscess, 16(32%)had Pneumonia, 10 (20%) had Sepsis and 8 (16%) had UTI.

Among 15 Diabetic foot subjects 7 (46.7%) had DKA and 8 (53.3%) had Diabetic Foot.

1 case who had Perianal abscess had HHS, Out of 16 Pneumonia subjects 9 (56.2%) had DKA and 16 (43.8%) had HHS.

Out of 10 subjects who had sepsis 8 (80%) had HHS and 2 (20%) had DKA. UTI was there in 4 (50%) of DKA and HHS subjects respectively.

There was no significant association between Infectious Precipitating factors and Hyperglycemic emergencies.

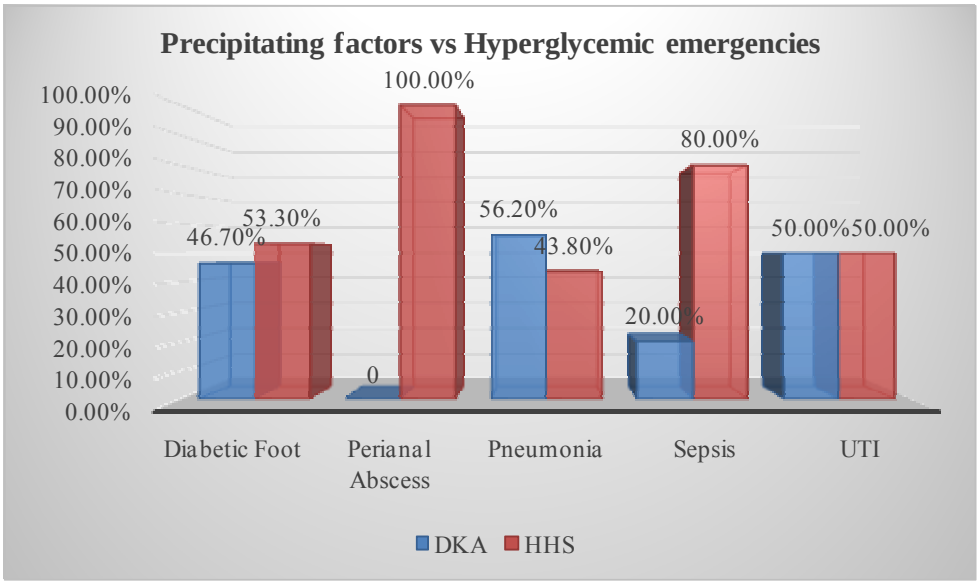

Figure 6: Bar diagram showing association between Infectious Precipitating factors and hyperglycemic emergencies

Table 7: Compliance of treatment among subjects with Hyperglycemic emergency in Diabetes

Drug compliance	Emergency				Total	
	DKA		HHS			
	No	%	No	%	No	%
Both OHA and Insulin discontinued	2	15.4%	11	84.6%	13	26.0%
Insulin discontinued	13	59.1%	9	40.9%	22	44.0%
OHA discontinued	6	54.5%	5	45.5%	11	22.0%
No discontinuation of treatment	1	25.0%	3	75.0%	4	8.0%
Total	22	44.0%	28	56.0%	50	100.0%

$\chi 2 = 7.436$, df=3, p =0.059

In the study among 50 subjects 13 (26%) had Poor compliance for Both Insulin and Oral hypoglycemic agents, 22 (44%) had poor compliance for only insulin and 11 (22%) had poor compliance for only Oral hypoglycemic agents. 4 (8%) had good compliance to treatment.

Among 13 subjects with poor compliance for both insulin and OHA, 2 (15.4%) had DKA and 11 (84.6%) had HHS.

Among 22 subjects with poor compliance for Insulin majority i.e. 13 (59.1%) had DKA and 9 (40.9%) had HHS.

Similarly among 11 subjects with poor compliance for OHA, 6 (54.5%) had DKA and 5 (45.5%) had HHS.

There was no significant association between treatment compliance and type of Hyperglycemic emergency.

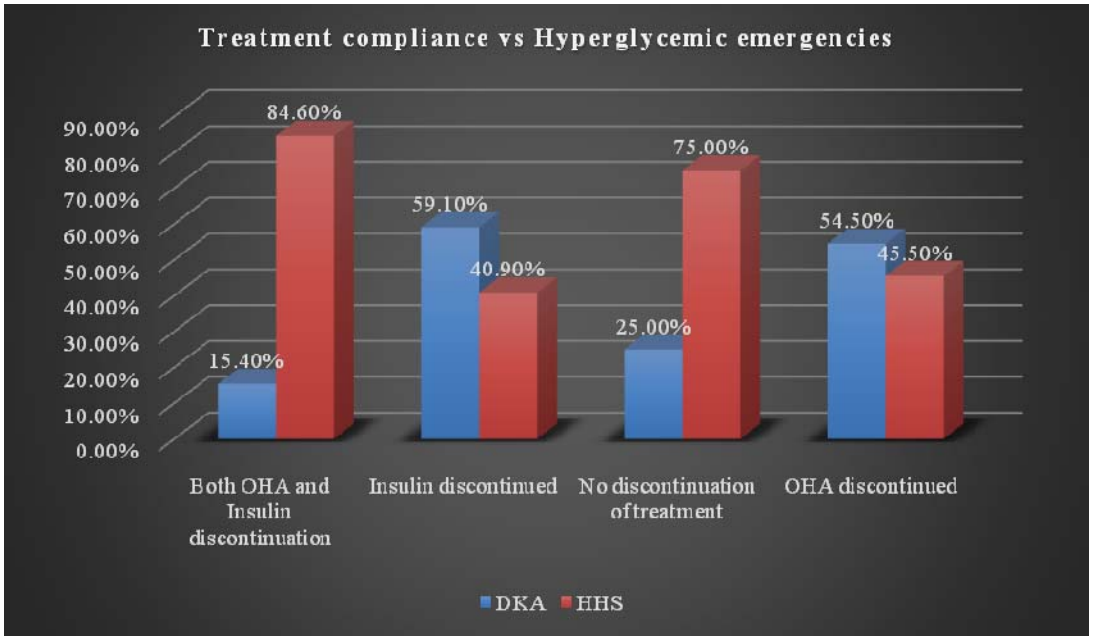

Figure 7: Bar diagram showing association between treatment compliance and hyperglycemic emergencies

Table 8: Association between HTN and Hyperglycemic emergency in Diabetes

		Emergency					
		DKA		HHS		Total	
		No	%	No	%	No	%
Hypertension	**No**	15	65.2%	8	34.8%	23	46.0%
	Yes	7	25.9%	20	74.1%	27	54.0%
Total		22	44.0%	28	56.0%	50	100%

$\chi 2 = 7.78$, df=1, p =0.005**

In the study among 50 subjects, 27 (54%) had hypertension and 23 (46%) were normotensive patients.

Among 27 Hypertensive subjects, 20 (74.1%) had HHS and 7 (25.9%) had DKA. This observation was statistically significant. I.e. HHS was commonly associated with Hypertension.

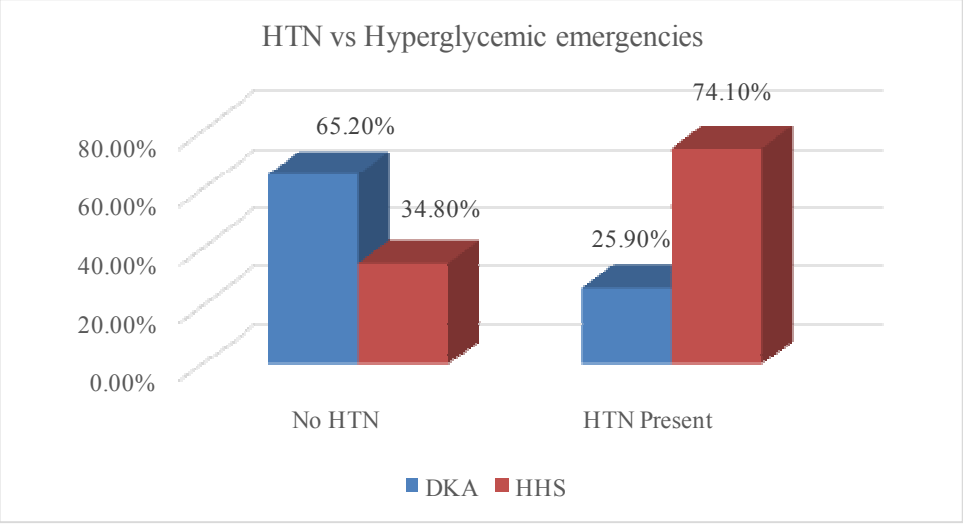

Figure 8: Bar diagram showing association between HTN and hyperglycemic emergencies

Table 9: Association of Complications among subjects with Hyperglycemic emergency in Diabetes

	Emergency				Total		p value
	DKA (n=22)		HHS (n=28)				
	No	%	No	%	No	%	
Retinopathy	9	40.9%	13	59.1%	22	44.0%	0.696
Nephropathy	4	40.0%	6	60.0%	10	20.0%	0.776
Neuropathy	2	50.0%	2	50.0%	4	8.0%	0.801
CAD	2	15.4%	11	84.6%	13	26.0%	0.016**
CVA	1	25.0%	3	75.0%	4	8.0%	0.425

In the study among 50 subjects, 22 (44%) had Retinopathy, 10 (20%) had Nephropathy, 4 (8%) had Neuropathy, 13 (26%) had CAD and 4 (8%) had CVA.

Among 22 subjects, 9 (40.9%) had DKA and 13 (59.1%) had HHS. Out of 10 subjects of Nephropathy 4 (40%) had DKA and 6 (60%) had HHS. Out of 4 Neuropathy subjects 2 (50%) of them had DKA and HHS respectively. Among 13 CAD subjects 11 (84.6%) had HHS and 2 (15.4%) had DKA. Similarly out of 4 subjects of CVA 3 (75%) had HHS and 1 (25%) had DKA.

CAD is more common among patients with HHS than DKA.

Statistical significance was found only for CAD in hyperglycemic emergencies. I.e. CAD was more commonly associated with HHS than DKA.

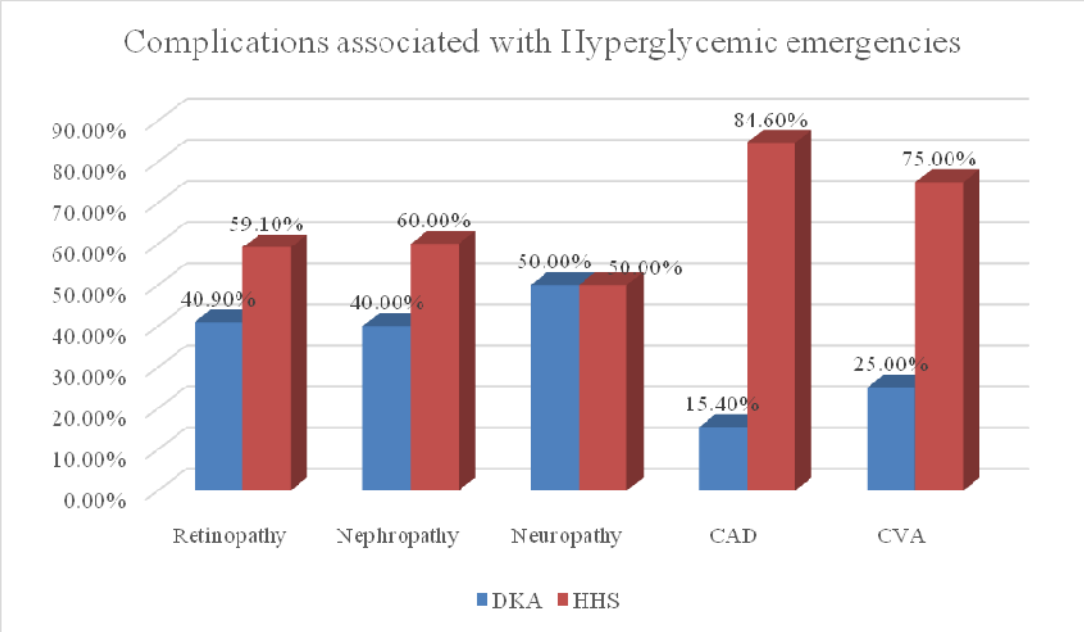

Figure 9: Bar diagram showing association between complications and hyperglycemic emergencies

From the fig it can observed that complications were commonly seen in HHS group than DKA group.

Table 10: Association between Sodium and Hypeglycemic emergencies

		Emergency				Total	
		DKA		HHS			
		No.	%	No.	%	No.	%
Na	>145(meq/l)	1	14.3	6	85.7	7	14
	135 to 145(meq/l)	4	57.1	3	42.9	7	14
	<135 (meq/l)	17	47.2	19	52.8	36	72
Total		22	44.0%	28	56.0%	50	100%

$\chi 2 = 3.151$, df=2, p =0.207

It was observed that out of 50 subjects, 7 (14%) had hypernatremia, 7 subjects (14%) had normal sodium levels and 36 (72%) had Hyponatremia.

Out of 7 Hypernatremia subjects, 6 (85.7%) had HHS and 1 patient (14.3%) had DKA, similarly in 7 subjects with normal sodium levels, 4 (57.1%) had DKA and 3 (42.9%) had HHS. Out of 36 Hyponatremia subjects 19 (52.8%) had HHS and 17 (47.2%) had DKA.

There was no significant association between Na levels and type of emergency.

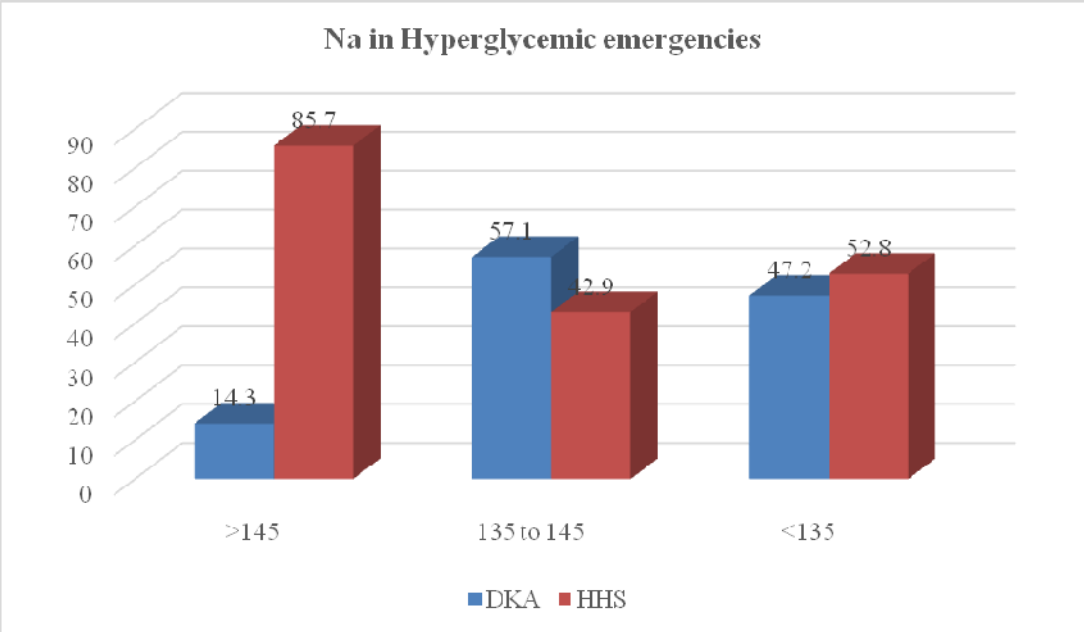

Figure 10: Bar diagram showing association of sodium in Hyperglycemic emergencies

Table 11: Association between Serum osmolality and Hyperglycemic emergencies.

		Emergency				Total	
		DKA		HHS			
		N(22)	%	N(28)	%	n	%
Serum osmolality	<320 (mosm/kg)	22	100%	0	0	22	44.0%
	321 to 340	0	0	2	7.1%	2	4.0%
	>340	0	0	26	92.9%	26	52.0%
Total		22	44%	28	56%	50	

$\chi 2$ =50.0, df=2, p <0.0001**

It was observed that out of 50 subjects, 22 (44%) subjects had DKA with Serum osmolality <320 msom/kg,and remaining 28(66%) had HHS with Serum Osmolality of 321 to 340 mosm/kg in 2 (4%) subjects and 26(52%) subjects with serum osmolality >340 mosm/kg.

Out of 28 HHS subjects 2(7.1%) had Serum Osmolality of 321 -340 and 26 (92.9%) had Serum Osmolality >340mosm/kg.

There was significant association between Serum osmolality and type of emergency

Table 12: Outcome among subjects with Hyperglycemic emergency in Diabetes

		Emergency				Total	
		DKA		HHS			
		No	%	No	%	No	%
Outcome	Survived	21	44.7%	26	55.3%	47	94.0%
	Mortality	1	33.3%	2	66.7%	3	6.0%
Total		22	44%	28	56%	50	100

$\chi 2$ = 0.147, df=1, p =0.701

In the study out of 50 subjects who presented with Hyperglycemic emergencies 47 (94%) recovered during treatment and only 3 subjects (6%) had mortality.

Among 47 subjects who recovered, 21 (44.7%) were DKA subjects and 26 (55.3%) were HHS subjects. Out of 3 subjects who succumbed death 1 (33.3%) had DKA and 2 (66.7%) had HHS. There was no significant difference on mortality with respect to DKA and HHS. I.e. in both emergencies subjects recovered after treatment.

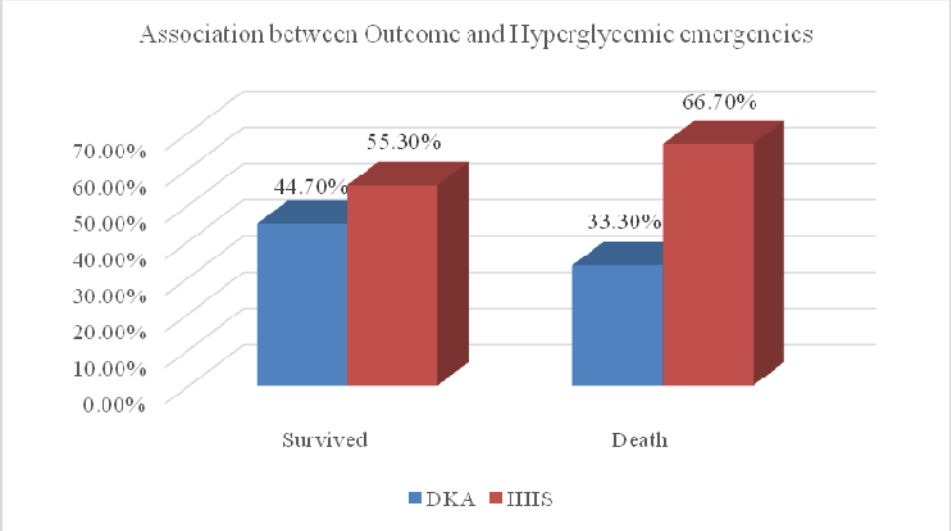

Figure 11: Bar diagram showing association between outcome and hyperglycemic emergencies Factors associated with outcome

Table 13: Association between age and Outcome among subjects with Hyperglycemic emergency in Diabetes

Age	DKA outcome				HHS outcome			
	Death (n=1)		Survived (n=21)		Death (n=2)		Survived (n=26)	
	n	%	n	%	n	%	n	%
<30 yrs	0	0	7	100.0%	0	0	1	100.0%
31 to 40 yrs	0	0	5	100.0%	0	0	2	100.0%
41 to 50 yrs	0	0	3	100.0%	0	0	2	100.0%
51 to 60 yrs	0	0	5	100.0%	1	12.5%	7	87.5%
>60 yrs	1	50.0%	1	50.0%	1	6.7%	14	93.3%
Total	1	4.5%	21	95.5%	2	7.1%	26	92.9%
p value	0.033*				0.947			

In the study out of 22 DKA subjects 21 (95.5%) recovered and only 1 patient (4.5%) succumbed death. Similarly out of 28 HHS subjects 26 (92.9%) recovered and 2 (7.1%) succumbed death. Hence mortality was slightly higher in HHS group.

All the subjects of DKA in the age group <30 yrs, 31 to 40 yrs, 41 to 50 yrs and 51 to 60 yrs recovered after treatment. Similarly all the subjects of HHS in the age group <30 yrs, 31 to 40 yrs and 41 to 50 yrs recovered.

In DKA, 2 subjects were in the age group > 60 yrs among them one (50%) recovered and one (50%) succumbed death. Similarly in HHS subjects out of 8 in age group 51 to 60 yrs, 7 subjects (87.5%) recovered and only 1 patient (12.5%)

succumbed death. Among 15 subjects in age group > 60 yrs, 14 subjects (93.3%) recovered and only 1patient (6.7%) succumbed death.

There was significant association between outcome and age in DKA group and there was no statistical significance in HHS group.

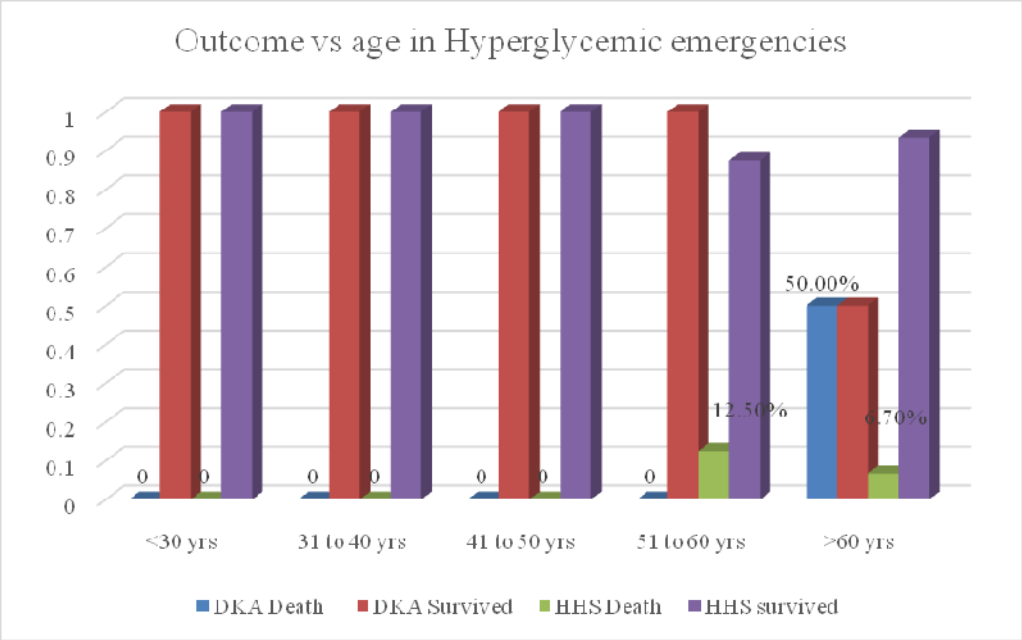

Figure 12: Bar diagram showing association Outcome and age in Hyperglycemic emergencies

Table 13: Association between Sex and Outcome among subjects with Hyperglycemic emergency in Diabetes

Sex	DKA outcome				HHS outcome			
	Death (n=1)		Survived (n=21)		Death (n=2)		Survived (n=26)	
	n	%	n	%	n	%	n	%
Female	0	0	12	100.0%	0	0	6	100.0%
Male	1	10.0%	9	90.0%	2	9.1%	20	90.9%
Total	1	4.5%	21	95.5%	2	7.1%	26	92.9%
p value	0.262				0.443			

All the 12 female DKA subjects (100%) recovered after treatment and out of 10 male subjects 9 (90%) recovered and only 1 (10%) succumbed death.

Similarly all the 6 female HHS subjects (100%) recovered after treatment and out of 22 male subjects20 (90.9%) survived and only 2 (9.1%) succumbed death.

There was no significant association between sex and outcome between two emergencies.

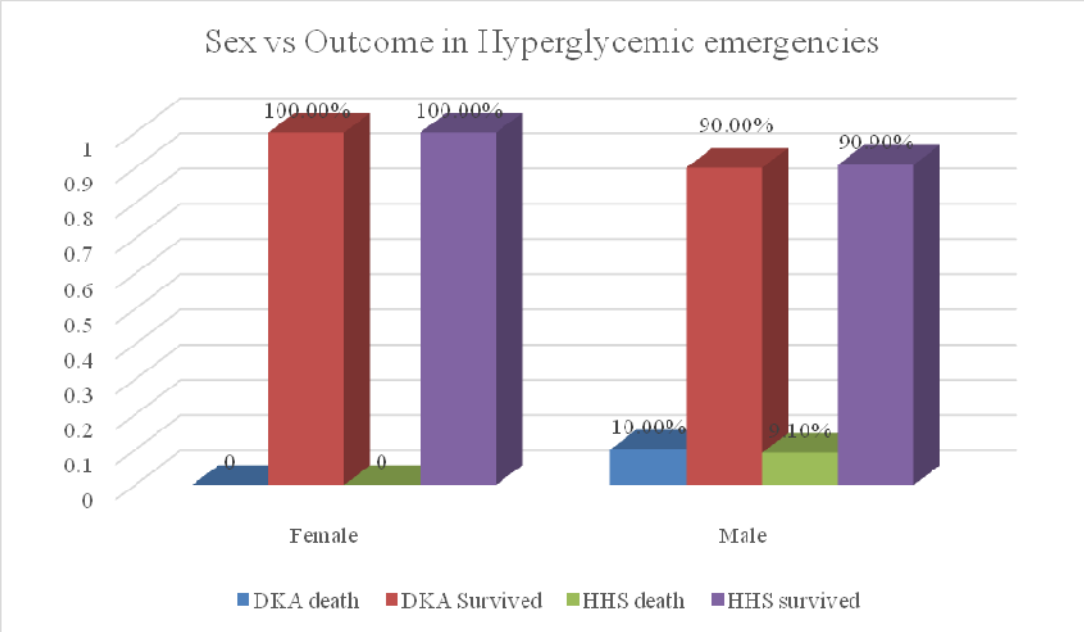

Figure 13: Bar diagram showing association between Sex and Outcome in Hyperglycemic emergencies

In the study it was observed that 6% who succumbed death were males in both the groups.

Table 15: Association between Infectious Precipitating factors and Outcome among subjects with Hyperglycemic emergency in Diabetes

Precipitating factors	DKA outcome				HHS outcome			
	Death (n=1)		Survived (n=21)		Death (n=2)		Survived (n=26)	
	n	%	n	%	n	%	n	%
Diabetic foot	1	14.3%	6	85.7%	0	0	8	100.0%
Pneumonia	0	0	9	100.0%	0	0	7	100.0%
Sepsis	0	0	2	100.0%	2	25.0%	6	75.0%
Urinary tract infection	0	0	4	100.0%	0	0	4	100.0%
Perianal abscess	0	0	0	0	0	0	1	100.0%
Total	1	4.5%	21	95.5%	2	7.1%	26	92.9%
p value	0.523				0.250			

In the study among DKA subjects7 had diabetic foot, of which 6 subjects (85.7%) survived and only one patient (14.3%) succumbed death. There were no other infectious precipitating factor for death among DKA patients.

Among HHS subjects out of 8 Sepsis subjects 6 (75%) survived and 2 patients (25%) died.

Hence in DKA diabetic foot was the precipitating factor for mortality of one patient and in HHS group sepsis was the precipitating factor for mortality in two subjects.

There was no significant association between precipitating factors and outcome.

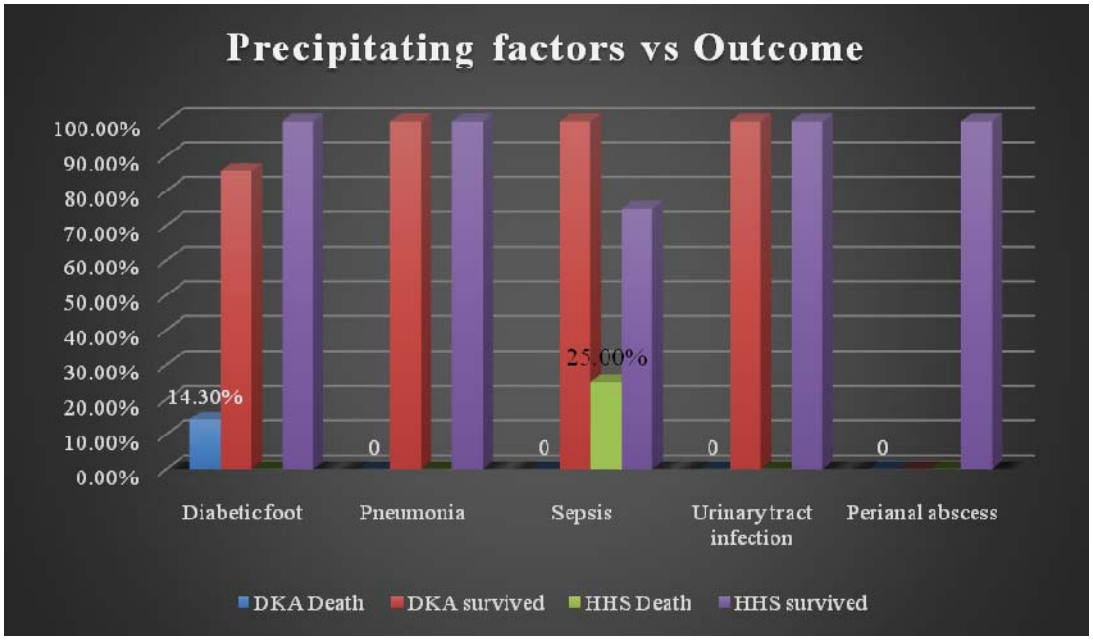

Figure 14: Bar diagram showing association between precipitating factors and outcome

Table 16: Association between Compliance of treatment and Outcome among subjects with Hyperglycemic emergency in Diabetes

Compliance of treatment	DKA outcome				HHS outcome			
	Death (n=1)		Survived (n=21)		Death (n=2)		Survived (n=26)	
	n	%	n	%	n	%	n	%
Both Insulin and OHA discontinued	1	50.0%	1	50.0%	0	0	11	100.0%
Insulin discontinued	0	0	13	100.0%	1	11.1%	8	88.9%
OHA discontinued	0	0	6	100.0%	1	20.0%	4	80.0%
No discontinuation of treatment	0	0	1	100.0%	0	0	3	100.0%
Total	1	4.5%	21	95.5%	2	7.1%	26	92.9%
p value	0.015**					0.469		

Out of 22 DKA subjects, 2 subjects had poor compliance for both Insulin and Oral hypoglycemic drugs. Among these two, one patient (50%) survived and one patient (50%) succumbed death.

No mortality occurred in subjects with history of only insulin discontinuation and only OHA discontinuation. This observation among DKA subjects was statistically significant.

Out of 28 HHS subjects, 9 had poor compliance for Insulin and 5 had poor compliance for OHA. Out of 9 subjects with poor compliance for Insulin 8 subjects (88.9%) survived and only 1 patient (11.1%) succumbed death. Similarly out of 5 subjects with poor compliance for OHA, 4 subjects (80%) recovered and only 1 patient (20%) succumbed death. There was no significant association between outcome and Drug compliance in HHS group.

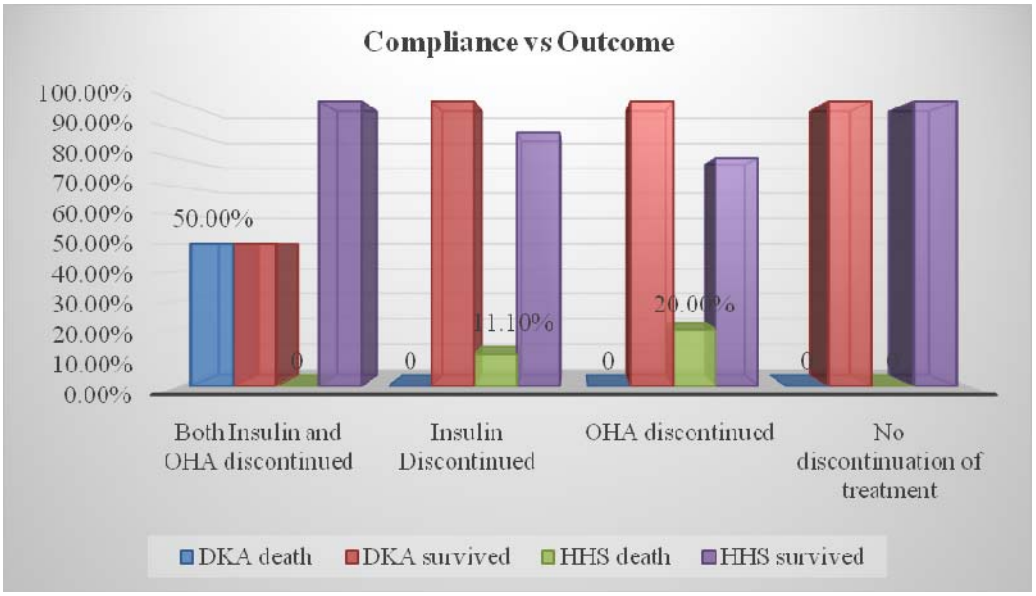

Figure 15: Bar diagram showing association between Compliance and Outcome in Hyperglycemic emergency

Table 17: Association between Hypertension and Outcome among subjects with Hyperglycemic emergency in Diabetes

Hypertension	DKA outcome				HHS outcome			
	Death (n=1)		Survived (n=21)		Death (n=2)		Survived (n=26)	
	n	%	n	%	n	%	n	%
No	0	0	15	100.0%	0	0	8	100.0%
Yes	1	14.3%	6	85.7%	2	10.0%	18	90.0%
p value	0.134				0.353			

Out of 22 DKA subjects 7 had hypertension, of which 6 subjects (85.7%) survived and only 1 patient (14.3%) succumbed death. Similarly out of 28 subjects of HHS 20 had hypertension, of which 18 subjects (90%) survived and only 2 subjects (10%) succumbed death. There was significant association between hypertension and outcome among hyperglycemic emergencies.

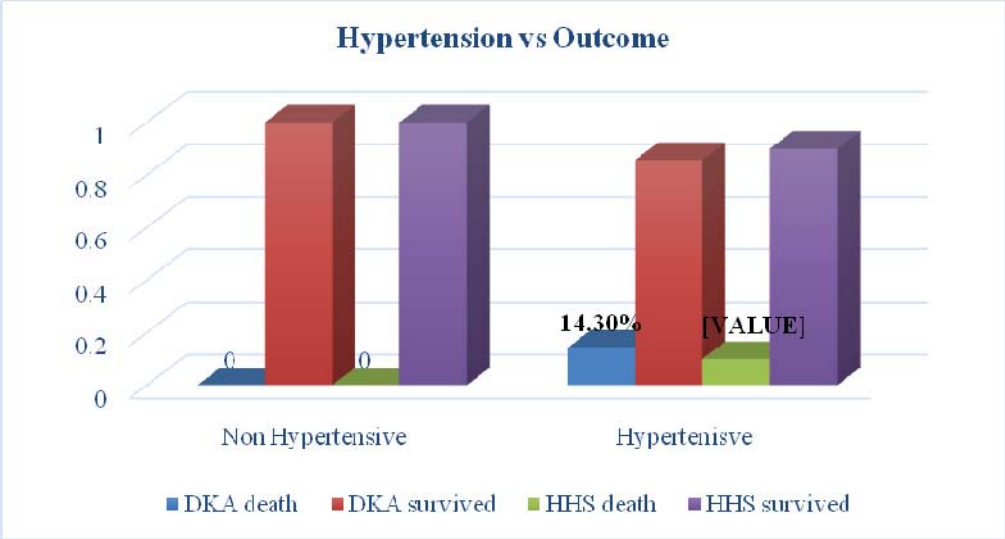

Figure 16: Bar diagram showing association between HTN and Outcome in Hyperglycemic emergencies

Table 18: Association between Complications and Mortality among subjects with Hyperglycemic emergency in Diabetes

	Complications	**Death (n =3)**
DKA	**CVA + Nephropathy**	1
HHS	**CAD + Retinopathy**	2

Among 22 subjects of DKA, there was one had mortality and 21 survived. One patient who succumbed death had CVA plus nephropathy as complication. In 28 HHS subjects there was 2 patients who had mortality and 26 survived. Two subjects who succumbed death had CAD plus retinopathy as complication.

Table 19: Quantitative Factors associated with Outcome among subjects with Hyperglycemic emergency in Diabetes

Mean values	DKA outcome			HHS outcome		
	Death (n=1)	Survived (n=21)	p value	Death (n=2)	Survived (n=26)	p value
Age (yrs)	75	40.38±14.2	0.028*	61.5 ± 9.1	63.1 ± 14.9	0.888
Duration of DM (yrs)	24	8.14 ± 3.5	<0.001**	14.5 ± 0.7	15.23 ± 6.3	0.874
RBS (mg/dl)	422	456 ± 62.8	0.603	600 ± 0.0	600 ± 0.0	1.00
HbA1c%	12.4	11.43 ± 1.22	0.450	11.9 ± 1.5	12.24 ± 1.2	0.692
Blood Urea(mg/dl)	62	36.71 ± 12.1	0.055	30.5 ± 3.5	42.6 ± 13.5	0.222
Serum Creatinine(mg/dl)	0.6	0.78 ± 0.24	0.470	1.1 ± 0.14	0.82 ± 0.28	0.194
Na+ (meq/l)	124	132 ± 7.64	0.319	123.5 ± 0.7	134.6 ± 12.1	<0.001*
K+ (meq/l)	2.6	3.88 ± 1.25	0.331	2.8 ± 0.28	4.08 ± 1.18	0.008*
PH	7.11	7.14 ± 0.03	0.443	7.39 ± 0.1	7.39 ± 0.1	1.00
Serum Osmolality (mosm/kg)	310.0	312.8 ± 3.6	0.466	338.0 ± 0.0	348.1 ± 4.6	0.005**
Insulin Requirement (units)	46	58.76 ± 12.1	0.312	92.5 ± 30.4	104.3 ± 20.9	0.455

In the study Age and duration were the predictors for Mortality in DKA subjects and Na+, K+ levels and Serum Osmolality were the predicting factors for mortality in HHS patients. Other factors were not significantly predicting the outcome in hyperglycemic emergencies in DM.

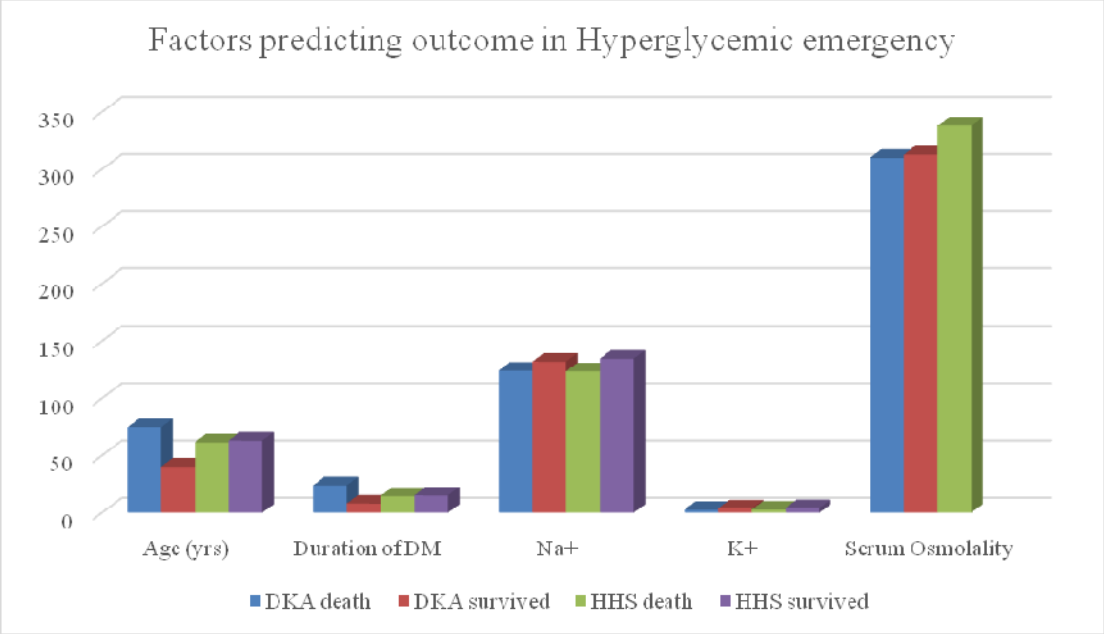

Figure 17: Bar diagram showing factors predicting outcome in hyperglycemic emergencies

DISCUSSION

Incidence:

In our hospital the total number of admission in the year 2013 was 3010 in medical wards. Out of that there were 608 diabetics, constituting 20.12% of the total admissions. Out of 608 Diabetics, 50 patients who developed Hyperglycemic Emergencies were included in this study. Out of which 32 were males and 18 were female patients.

Incidence of Hyperglycemic emergencies in our study was 8.22 %. Diabetic Ketoacidosis(DKA) was 44 % and Hyperglycemic hyperosmolar non ketotic state(HHS) was 56%.

A study by Chung et al[80] showed incidence of DKA is 4.6 to 8.0 per 1000 person-years, whereas that of HHS is less than 1 per 1000 person-years.

A study by Ogbera et al[81] showed that Hyperglycaemic emergencies (HE) account for 40% of all DM related hospitalization with a preponderance of DKA admissions compared to that of HHS.

In contrast to these studies, this study showed higher incidence of HHS, because more of Type 2 DM subjects were included in this study.

Age:

In this study the minimum age was 24 years and the maximum age was 88 years. The mean age was 54 years. It was observed that majority of DKA cases 87.5% were found in less than 30 years age group and HHS was common after 60 yrs of age (88.2%) .

This was observed because Type 1 DM patients were more in DKA and Type 2 DM patients more in HHS.

A study by Chung ST et al[84] the age range of HEs was between 36 to 64 years with mean age of 54 years**.**

Several other studies have reported that the average age of patients admitted for HHS was 40 to 70 years.[83,84,86]

In a study by Chu CH et al. patients with DKA were between the ages of 18 and 44 years (56%) and 45 and 65 years (24%), with only 18% of patients <20 years of age{**82}.**

The above studies correlates with the present study**.**

Sex:

In the study 18 (36%) were females and 32 (64%) were males. It was observed that Majority of females presented with DKA 12 (66.7%) and majority of males presented with HHS 22 (68.8%).

Louis Vignati et al.[91] has shown a higher incidence of HEs in women compared to men with DKA more in females and HHS more in males.

The above study correlates with this study.

Type of diabetes among subjects with Hyperglycemic emergency in Diabetes

In the study 15 (30%) had type 1 DM and 35 (70%) had type 2 DM. It was observed that DKA was more common among Type 1 DM (80%) and HHS was common among Type 2 DM (71.4%).

Edo AE et al[94] study reported DKA predominant in Type 1 DM and HHS predominant in Type 2DM.

This study correlates with the Edo AE et al study**.**

Duration of diabetes:

Mean duration of diabetes was high among HHS (15years) than DKA group(8 years). I.e more the duration of diabetes risk for HHS is high. Type 1 DM is common among younger individuals mean duration of diabetes among DKA was lower than HHS group.

In a study by Patel JC et al[93] reported, the duration of diabetes varied in the following manner: Up to 1 year incidence of HEs was 2.2%, 1 – 5 years 2.8%, 6 – 10 yrs 2.9% and >10 yrs 4.3%.

This study correlates with the above study.

Precipitating Factors:

In the present study, the commonest precipitating factor was infection followed by discontinuation of treatment .

Amongst infections, Pneumonia was the commonest in DKA cases(40.9%) and Sepsis and Diabetic foot was the commonest among HHS cases (28.5%). Infection was high due to decreased immunity and comorbid conditions. Documented reasons for poor drug compliance may be due to poor accessibility to health facilities, high costs of drugs often resulting from polypharmacy because of co-morbidities and also ignorance on self care habits of DM.[83]

In various studies infection was main precipitating factor followed by poor drug compliance.[85,86]

In a study by Ogbera et al[84] poor drug compliance was a major precipitant.

This study correlates with the above studies.

Clinical Profile

In this study 52% had vomiting, 28% had Nausea, 6% had dehydration, 14% had altered sensorium, 14% had abdominal pain, 8% had tachycardia and 18% had acidotic breathing.

It was observed that all the symptoms were common among HHS patients except for acidotic breathing which was common with DKA patients (88.9%).

In a study by Jean Louis Chaisson et al.[87] the clinical features of DKA were :- nausea (83.4%), vomiting (78.5%) and abdominal pain (51%).

A study reported by Pinnies JA et al.[88] abdominal pain and vomiting as the predominant clinical features of HHS.

The above studies correlates with the present study.

Biochemical Profile:

Mean RBS in DKA group was 454 mg/dl and HHS group was 600 mg/dl.

pH mean for DKA was 7.13 ± 0.03 and mean for HHS was 7.39±0.06

K value mean for DKA was 3.823 ± 1.25 meq/l and mean for HHS was 3.99±1.19 meq/l

Na value mean for DKA was 131.64 ±7.65 meq/l and mean for HHS was 133.89±11.97 meq/l.

Urea value mean for DKA was 37.86 ±12.9 mg/dl and mean for HHS was 41.82±13.42mg/dl.

Mean PH was lower among DKA patients than HHS group because of acidosis.

Mean Serum Osmolality among DKA patients was lower than in HHS patients.

Increased levels of blood sugars in HHS patients than DKA reported to be associated with unprovoked ketoacidosis, and the suggested mechanism is glucotoxicity to the beta cell.[81]

Electrolyte imbalances are the consequences of hyperglycemia, hyperosmolality, and acidosis. The biochemical parameters noted in this study were those of hypokalaemia. hyponatraemia, hypernatraemia and azotaemia and hyperkalaemia.[83]

These abnormalities occurred more in people with HHS. Hypernatremia (85.7%) and Hyponatremia (52.8%), Hypokalemia (54.2%) and azotemia (62.5%) more in HHS patients. Hyperkalemia high in DKA cases (58.2%). Hyponatremia was the prevalent form of electrolyte abnormality (72%).

Pinto ME et al.[84] study reported Biochemical abnormalities occurred more in people with DKA except for hypernatraemia (HN) and hypokalaemia (HP) which occurred in higher percentages of subjects with HHS viz (12%,47% in HHS vs 2%,35% in DKA). Hypokalemia was the prevalent form of electrolyte imbalance.

The above study was in contrast to the present study as more subjects presented with increased dehydration.

Hypokalaemia occurs as a a result of urinary losses in the face of a high osmotic gradient.[83]

Hyponatraemia, often result from urinary losses and may be dilutional as water shifts extracellularly because of high serum osmolarity.[83]

Hyperkalemia is explained by a shift of potassium from the intracellular to extracellular space because of acidosis from insulin deficiency and decreased renal tubular secretion.[83]

Azotemia which may be a resultant effect of volume contraction in patients with HEs. Hypernatraemia, may signify a response to reduction in circulating volume.[83]

Anumah et al.[94] study reported higher levels of Serum Osmolality in HHS patients than in DKA patients.

The above study correlates with the present sudy.

Hyperosmolality was due to hyperglycemia and water deficit.[90]

Factors Predicting the Outcome in Hyperglycemic Emergencies:

- In this study Age and duration of DM were the predictors for Mortality in DKA patients and abnormal levels of Sodium (both hypo and hypernatremia), Potassium (both hypo and hyperkalemia) and Increased Serum Osmolality were the predicting factors for mortality in HHS patients. Other factors were not significantly predicting the outcome in hyperglycemic emergencies in DM.

A study by Stamatis P et al[90] on mortality prediction model in diabetic ketoacidosis reported the following as the predictors of mortality. These were severe co-existing diseases, Age, Duration of DM, pH <7.0 at presentation, units of insulin required in first 12 hrs >50 and serum glucose >300mg/dl after 12 hrs, depressed mental state and fever after 24 hrs.

A study by . Pinnies JA et al[89] reported that septic shock was the most frequent cause of death (31%) and poor prognostic indicators were, older age, hypotension, low Na, pH and HCO3,Increased Serum Osmolality and high urea in HHS patients.

A study by Chung ST et al.[82] reported Abnormal levels of Sodium and Potassium predictive factors for outcome in HHS

The studies of Stamatis P, Pinnies JA and Chung ST correlates with the present study.

CONCLUSION

- Incidence of Hyperglycemic emergencies among Diabetic patients was 8.22 %. Diabetic Ketoacidosis (DKA) was 44 % and Hyperglycemic hyperosmolar nonketotic state (HHS) was 56%.
- Majority of DKA cases were found in less than30 yrs age group and HHS were common after 60 years of age .
- Among Hyperglycemic emergency patients studied 36% were women and 64% were men. Majority of women presented with DKA and majority of men presented with HHS.
- 30% had type 1 DM and 70% had type 2 DM. It was observed that DKA (was more common among Type 1 DM and HHS was common among Type 2 DM.
- Most common presenting clinical features were vomiting, Nausea, dehydration, altered sensorium, abdominal pain, tachycardia and acidotic breathing. All the symptoms were common among HHS patients except for acidotic breathing which was common with DKA patients.
- Mean duration of diabetes was high among HHS (15years) than DKA group(8 years).
- Commonest precipitating factor was infection followed by discontinuation of treatment . Amongst infections, Pneumonia was the commonest in DKA cases and Sepsis and Diabetic foot was the commonest among HHS patients.
- The biochemical parameters noted in this study were those of hypokalaemia. hyponatraemia, hypernatraemia and azotaemia and hyperkalaemia. These abnormalities occurred more in people with HHS. Hyponatremia was the prevalent form of electrolyte abnormality in hyperglycaemic emergencies.

- Mean Serum Osmolality among DKA patients was lower than in HHS patients.
- Some of the clinical and biochemical parameters which indicate bad prognosis were age, duration of diabetes, RBS at admission, PH, Insulin requirement and comorbid conditions.
- Age and duration were the predictors for Mortality in DKA patients and abnormal levels of Sodium (both hypo and hypernatremia), Potassium (both hypo and hyperkalemia) and Increased Serum Osmolality levels were the predicting factors for mortality in HHS patients.

SUMMARY

50 patients admitted to R.L JALAPPA Hospital, Tamaka, Kolar attached to Sri Devraj URS Medical College with Hyperglycemic Emergencies during the period of January 2013 to December 2013 were studied. Patients were studied with respect to age, sex, type of diabetes mellitus, incidence, precipitating factors, the clinical and biochemical profiles and insulin therapy and Outcome of Hyperglycemic Emergencies.

1. Incidence of Diabetic Ketoacidosis was 44 % and Hyperglycemic hyperosmolar non ketotic state was 56% during this period.
2. Majority of DKA subjects were found in less than 30 years age group and HHS subjects were common after 60 years of age.
3. Majority of women presented with DKA and majority of men presented with HHS.
4. It was observed that DKA was more common among Type 1 DM and HHS was common among Type 2 DM.
5. All the symptoms were common among HHS patients except for acidotic breathing which was common with DKA patients.
6. Commonest precipitating factor was infection followed by discontinuation of treatment.
7. The biochemical parameters noted in this study were those of hypokalaemia. hyponatraemia, hypernatraemia and azotaemia and hyperkalaemia. These abnormalities occurred more in people with HHS. Hyponatremia was the prevalent form of electrolyte abnormality.
8. Mean Serum Osmolality among DKA patients was lower than in HHS group.

9. Cinical and biochemical parameters which may indicated bad prognosis were age, duration of diabetes, RBS at admission, PH , Insulin requirement and comorbid conditions..
10. Age and duration were the predictors for Mortality in DKA patients and abnormal levels of Sodium (both hypo and hypernatremia), Potassium (both hypo and hyperkalemia) and Increased Serum Osmolality levels were the predicting factors for mortality in HHS patients.

BIBLIOGRAPHY

1. Johnson DD, Palumbo PJ, Chu C, et al. Diabetic ketoacidosis in a communitybased population. Mayo Clin Proc 1980; 55 : 83-88.

2. Faich GA, Fishbein HA, Ellis SE, et al. The epidemiology of diabetic acidosis: a population-based study Am J Epidemiol 1983;117: 551-558.

3. Fishbein HA, Palumbo PJ, et al. Acute metabolic complications in diabetes. InDiabetes in America. National Diabetes Data Group, National Institutes of Health, 1995, p.283 -291 (NIH publ. no.: 95-1468).

4. Umpierrez GE, Kelly JP, Navarrete JE, Casals MMC, Kitabchi AE, et al. Hyperglycemic crises in urban blacks. Arch Intern Med 1997;157 : 669-675.

5. Kitabchi AE, Fisher JN, Murphy MB, Rumbak MJ, et al. Diabetic ketoacidosis and the hyperglycaemic hyperosmolar nonketotic state. In Joslin's Diabetes Mellitus. 13th ed. Kahn CR, Weir GC, Eds. Philadelphia, Lea & Febiger,1994, p.738 -770.

6. International Textbook of Diabetes Mellitus, 2nd ed .Chichester; Willey, 1997; 109-124.API Text book of medicine, 7.th edition, page no.1097-1102.

7. Basu A, Close CF, Jenkis D, Krentz AJ, Nattraz .M, Wright AD, persisting mortality in Diabetic ketoacidosis, Diabet Med 10;282-284, 1997.

8. Dreschfeld J. the Bradshawe lecture on diabetic coma, BMJ 1886:2358-63.

9. National Diabetes Data group, Ed. Bethesda, MD, National Institute of Health, 1995, p 283-291(NIH pub.no.95-1468).

10. Della Manna T et al. Subcutaneous use of a fast acting insulin analog an alternative treatment for pediatric patient with DKA. Diabetic care 2011; 28: 1856 – 1861.

11. Bertram F. Pathogenese und prognose des coma. Diabeticum Ergeb Inn Med Kinder heilkd 1932; 43: 258- 365.

12. Kreisberg RA. Diabetic ketoacidosis, In: Rifkin H, Port D ads. Diabetes mellitus, theory and practice. 4th edition Asterdam Elsivier, 1990: 591-603.

13. Fishbein HA, Palumbo PJ: Acute complications of diabetes. In Diabetes in America. Narin's RG, Jones ER, Stom MC, et al. Diagnostic strategies in disorders of fluids, electrolytes, acid -base homeostasis. Am J Med 1982; 72: 496-520.

14. Rewers M, Norris JM, Eisenbarth GS, et al. Diabetes autoimmunity study in the young (DAISY). J Autoimmune 1996; 9:405-410.

15. Almind K, Doria A, Kahn CR. Putting the genes for type II diabetes on the map. Nat Med 2001; 7:277-279.

16. Gavin JR III, Alberti KGMM, Davidson MB, et al. Report of Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183-1197.

17. WHO Classification Consultation Group. Definition, diagnosis and classification of DM and its complications. 2nd Ed. WHO NCD/NCS/99 Geneva WHO, 1999; 1-59.

18. WHO Study Group. Diabetes Mellitus. Technical Report Series 727. Geneva WHO, 1985.

19. E nnis ED, Stahl EJVB, Kreisberg RA: The hyperosmolar hyperglycaemic syndrome. Diabetes Rev 1994; 2:115 -126.

20. Arieff AI, Carrol H: Nonketotic hyperosmolar coma with hyperglycemia:clinical features, pathophysiology, renal function, acid-base balance,plasma-cerebrospinal fluid equilibria, and the effects of therapy in 37cases. Medicine1972; 51:73 -94.

21. Kitabchi AE, Wall BM: Diabetic ketoacidosis. Med Clin North Am 1995;79:9-37.

22. Fishbein HA, Palumbo PJ: Acute metabolic complications in diabetes.In Diabetes in America. National Diabetes Data Group, National Institutes of Health, 1995, p. 283-291 (NIH publ. no.: 95-1468).

23. T he DCCT Research Group: Implementation of treatment protocols in the Diabetes Control and Complications Trial. Diabetes Care 1995; 18:361-376.

24. Weissman JS, Gatsonis C, Epstein AM: Rates of avoidable hospitalization by insurance status in Massachusetts and Maryland. JAMA 1992; 268:2388-2394.

25. Wolfsdorf J, Glaser N, Sperling MA. Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. Diabetes Care 2006; 29: 1150– 2259. [PubMed].

26. White NH. Diabetic ketoacidosis in children. Endocrinol Metab Clin North Am 2010; 29: 657– 682.[PubMed]

27. Graves EJ, Gillium BS. the National Center for Health Statistics Detailed diagnoses and procedures: National Hospital Discharge Survey, 2005. Vital Health Stat 131997;(130): 1– 146. [PubMed]

28. Malone ML, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. J Am Geriatr Soc 1992; 40: 1100– 1104. [PubMed]

29. Umpierrez GE, Kelly JP, Navarrete JE, Casals MM, Kitabchi AE. Hyperglycemic crises in urban blacks. Arch Intern Med 1997; 157: 669– 675. [PubMed]

30. Ennis ED, Stahl EJVB, Kreisberg RA. The hyperosmolar hyperglycemic syndrome. Diabetes Rev 1994; 2: 115–126.

31. Lorber D. Nonketotic hypertonicity in diabetes mellitus. Med Clin North Am 1995; 79: 39– 52. [PubMed]

32. Kitabchi AE, Fisher JN, Murphy MB, Rumbak MJ. Diabetic ketoacidosis and the hyperglycemic hyperosmolar nonketotic state. In Joslin's Diabetes Mellitus 13th ed Kahn CR, Weir GC, editors. Eds. Philadelphia, Lea & Febiger, 2011, p. 738– 770.

33. Genuth SM. Clinical remission in diabetes mellitus: Studies of insulin secretion.Diabetes 2010; 19:116-21.

34. Block MB, Mako ME, Steiner DF, Rubenstein AH. Diabetic ketoacidosis: Evidence for C-peptide and proinsulin secretion following recovery. J Clin Endocrinol Metab 1972; 35:402-6.

35. Kitabchi AF, Ayyagari V, Guerra SMO. The efficacy of low dose versus conventional therapy of insulin for treatment of diabetic ketoacidosis. Ann Intern Med 2008; 84:633-8.

36. Kipnis DM. Insulin secretion in diabetes mellitus. Ann Intern Med 2008; 69:891-901.

37. Kitabachi AE, Duckworth WC, Stentz FB. Diabetes Mellitus: Theory and Practice. 4th ed. Amsterdam: Elsevier, 1990.

38. Mahoney C. Extreme gestational starvation ketoacidosis: Case report. Am J Kidney Dis 1992; 20:276-280.

39. Abba SE, Kitabchi, Fisher JN. Joslin's Diabetes. 13th Edn.

40. Schade DS, Eaton RP, Alberti KG, et al. Diabetic coma: Ketoacidosis and non-ketotic hyperosmolar coma. 1st Ed. Albuguergue Univ of New Maxico Press, 1981.

41. Cohen AS, Vance VK, Runyan JW Jr. et al. Diabetic ketoacidosis: An evaluation of cause, course and therapy in 73 cases. Ann Intern Med 1960; 53:55-86.

42. Sacks HS, Shahshalami M, Kitabchi AE, et al. Similar responsiveness of diabetic ketoacidosis to low-dose insulin by intramuscular injection and albumin free infusion. Ann Intern Med 1979; 90:36-42.

43. Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. N Eng J Med 1983; 309:159-69.

44. Keller U. Diab Ketoacidosis: Current views on pathogenesis and treatment. Diabetologia 1986; 29:71-7.

45. Stentz FB, Umpierrez GE, Cuervo R, Kitabchi AE. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. Diabetes 2004; 53: 2079–2086.

46. Buyukasik Y, Ileri NS, Haznedaroglu IC, Karaahmetoglu S, Muftuoglu O, Kirazli S, Dundar S. Enhanced subclinical coagulation activation during diabetic ketoacidosis. Diabetes Care 1998;21:868–870.

47. Delaney MF, Zisman A, Kettyle WM. Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. Endocrinol Metab Clin North Am 2000; 29: 683–705.

48. Kitabchi AE, Fisher JN, Murphy MB, Rumbak MJ. Diabetic ketoacidosis and the hyperglycemic hyperosmolar nonketotic state. In Joslin's Diabetes Mellitus. 13th ed. Kahn CR, Weir GC, Eds. Philadelphia, Lea & Febiger, 1994, p. 738–770.

49. Nair S, Yadav D, Pitchumoni C. Association of diabetic ketoacidosis and acute pancreatitis: Observation in 100 patients of DKA. Am J Gastroenterol 2000; 95: 2795-2800.

50. Mahoney C. Extreme gestational starvation ketoacidosis: Case report. Am J Kidney Dis 1992; 20:276-280.

51. Munro J, Campbell I, McCuish A, et al. Euglycemic diabetic ketoacidosis. BMJ 2003; 9:578-580.

52. Franke B, Carr D, Hatem M. A case of euglycemic diabetic ketoacidosis in pregnancy. Diabet Med 2011; 18:858-859.

53. Kemperman F, Weber J, Gorgels J, et al. The influence of ketoacids on plasma creatinine assays in diabetic ketoacidosis. J Intern Med 2010; 248:511-517.

54. Adrogue HJ, Wilson H, Boyd AF, et al. Plasma acid-base pattern in diabetic ketoacidosis. N Eng J Med 1982; 307:1603-1610.

55. Cronin J, Kroops S, Diamond J. et al. Alkaemia in diabetic ketoacidosis. Am J Med 1984; 7:192-194.

56. Adrogue H, Barrero J, Eknoyan G. Salutary effects of modest fluid replacement in treatment of adults with diabetic ketoacidosis. JAMA 2010; 262:2108-2133.

57. Gebera B. Risk factors for cerebral edema in children with diabetic ketoacidosis. New Eng J Med 2001; 344-1556.

58. Alberti K. Low dose insulin in the treatment of diabetic ketoacidosis. Arch Intern Med 2011; 137:1367-1376.

59. Fort P, Waters S, Lifshitz F. Low dose insulin infusion in treatment of diabetic ketoacidosis: bolus versus no-bolus. J Paediatr 1980; 96:36-40.

60. Beigelman P. Potassium in severe diabetic ketoacidosis. Am J Med 2003; 54:419-420.

61. Morris L, Murphy M, Kitabchi A. Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med 1986; 105:836-840.

62. Kraut J, Kurtz I. Use of base in treatment of severe acidemic states. Am J Kidney Dis 2001; 38: 703-727.

63. Bohanon N. Large phosphate shifts with treatment for hyperglycemia. Arch Intern Med 1989; 149: 1423-1425.

64. Fisher J, Kitabchi A. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab 1983; 57: 177-180.

65. Brandenberg M, Dire D. Comparison of arterial and venous gas values in the initial emergency department evaluation of patients with diabetic ketoacidosis. Ann Emerg Med 2002; 31: 459-465.

66. Wallace T, Merton N, Gardner S, et al. The hospital and home use of a 30-second hand-held blood ketone meter: Guidelines for clinical practice. Diabet Med 2011; 18: 640-645.

67. Edge J, Hawkins M, Winter D, et al. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. Arch Dis Child 2001; 85: 16-22.

68. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2013; 29: 2739–2748.

69. Quigley R, Curran R, Stagl R, et al. Management of massive pulmonary thromboembolism complicating diabetic ketoacidosis. Ann Thorac Surg 1994; 57: 1322-1324.

70. Keenan HA, Costacou T, Sun JK, Doria A, Cavellerano J, Coney J, Orchard TJ, Aiello LP, King GL: Clinical factors associated with resistance to microvascular complications in diabetic patients of extreme disease duration: the 50-year medalist study. Diabetes Care 2009; 30: 1995-1997.

71. Fong DS, Aiello LP, Ferris FL 3rd, Klein R: Diabetic retinopathy. Diabetes Care 2006; 27: 2540–2553.

72. Gabbay KH: Aldose reductase inhibition in the treatment of diabetic neuropathy: where are we in 2004? Curr Diab Rep 2004; 4: 405–408.

73. Watkins PJ: Retinopathy. BMJ 2005; 326:924–926.

74. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T: Diabetic nephropathy: diagnosis, prevention, and treatment.Diabetes Care 2005; 28:164–176.

75. American Diabetes Association: Standards of medical care in diabetes—2007 [Position Statement]. Diabetes Care 2007; 30: S4–S41.

76. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. : Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care 2005; 28:956–62.

77. Boyle PJ: Diabetes mellitus and macrovascular disease: mechanisms and mediators. Am J Med 2007; 120:S12–S17.

78. Paterson AD, Rutledge BN, Cleary PA, Lachin JM, Crow RS: The effect of intensive diabetes treatment on resting heart rate in type 1 diabetes: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2013; 30: 2107–2112.

79. Fishbein H, Palumbo PJ: Acute metabolic complications in diabetes. In Diabetes in America. 2nd edition. Edited by Harris MI, C owie C C , Stern MP, et al. Bethesda (MD) National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, NIH Publication No.95-1468; 1995:283-292.

80. Ogbera AO, C hineneye S, Onyekwere A, Fasanmade O: Prognostic Indices of DM mortality. Ethn Dis 2007; 17(4):721-725. {PubMed Abstract}

81. Chu CH, Lee JK, Lam HC , Lu C C : Prognostic factors of hyperglycaemic hyperosmolar nonketotic state. Chang Gung Med J 2001; 24(6):345-351.

82. Chung ST, Perue GG, Johnson A, Younger N, Hoo CS, Pascoe RW: Predictors of hyperglycaemic crises and their associated mortality in Jamaica. Diabetes Res Clin Pract 2006; 73(2):184-190.

83. Ogbera AO, Jacob A, Chioma U, Olufemi F et al. BMC Endocrine Disorders 2009; 9: 9.

84. Pinto ME, Villena JE, Villena AE. Diabetic ketoacidosis in Peruvian patients with type 2 diabetes mellitus. Endocr Pract 2008; 14: 442‑6.

85. Rolfe M, Ephraim GG, Lincoln DC, Huddle KR. Hyperosmolar non‐ketotic diabetic coma as a cause of emergency hyperglycaemic admission to Baragwanath Hospital. S Afr Med J 1995; 85: 173‐6.

86. Christopher A, Newton MD, Philip Raskin. Diabetic ketoacidosis in type 1 & type 2 diabetes mellitus. Arch Inter Med 2004; 164:1925-31.

87. Jean Louis Chaisson, Nahla AJ, Raphael B, Sylvie B, et al. Diagnosis and treatment of diabetic ketoacidosis and hyperglycemic hyperosmolar state. CMAJ 2003; 168(7):859-66.

88. Pinnies JA, Cairo G, Gaztambide S, Vazquez JA. Course and prognosis of 132 patients with diabetic ketotic and non-ketotic hyperosmolar state. Diabetes Metab 1994 Jan-Feb; 20(1):43-8.

89. Stamatis P, Efstathiou, Aphrodite G, Tsioulos, Loannis et al. A mortality prediction model in diabetic ketoacidosis. Clin Endocrinol 2002; 57:595-601.

90. Louis Vignati. Coma in Diabetes. Cader Asmac Joslin's Diabetes Mellitus. 12th Ed. Lea and Febiger, 526-552.

91. Jennifer W and Martin JA. Diabetic ketoacidosis and hyperosmolar hyperglycemic state. Joslin's Diabetes Mellitus. 14thEd.

92. Patel JC, Dhirawani MK, Kapekar SG. Analysis of 5481 subjects of diabetes mellitus. Diabetes in Tropics; 94-99.

93. Edo AE.Clinical profile and outcomes of adult patients with hyperglycemic emergencies managed at a tertiary care hospital in Nigeria. Niger Med J 2012 Jul;53(3):121-5.

94. Anumah F, Ohwovoriole A. Serum biochemistry in Nigerians with hyperglycaemic emergencies. Ethn Dis. 2008 ;18: 26–30.

ANNEXURES

PROFORMA

CASE HISTORY OF THE PATIENTS

Case No : Date:

Name: OP No/ IP No:

Age:

Gender: Occupation:

Date of Admission:

Date of Discharge/Death:

CHIEF COMPLAINTS:

PAST HISTORY:

History of diabetes – since

Type of Diabetes-

Any major illness in the past

Similar history in the past

TREATMENT HISTORY:

H/O Discontinuation of Insulin /Antidiabetic drugs

FAMILY HISTORY:

H/o Diabetes mellitus in the family

PERSONAL HISTORY:

Diet

Appetite

Bowels

Micturation

Smoking

Alcohol

GENERAL PHYSICAL EXAMINATION:

Appearance:

Signs of Dehydration:

Ht: Wt: BMI:

Pulse rate : Blood pressure :

Respiratory rate: Temperature:

Oedema : Icterus :

Pallor : Clubbing :

Cyanosis : Koilonychia:

Lymphadenopathy :

SYSTEMIC EXAMINATION :

Cardiovascular system:

Respiratory system:

Per Abdomen :

Central Nervous system:

DIAGNOSIS :

INVESTIGATIONS :

Haemogram:

Random Blood Sugar at admission:

Glycated haemoglobin:

Urine examination: Urine ketone bodies:

Arterial Blood Gas Analysis:

Seum Osmolality:

Blood Urea: Serum Creatinine:

Sodium: Potassium:

Bicarbonate:

Anion gap:

Chest Radiograph:

Electrocardiograph:

Fundus Examination:

Others:

Complications:

MASTER CHART

Sl No.	NAME	HOSPITAL NO.	AGE(YEARS)	CLINICAL FEATURES	Gender	Type of DM	DURATION OF DM	PRECIPITATING FACTORS	OHA OMISSION	INSULIN OMISSION	HTN (Y/N)	RBS at admission	HbA1c%	BU(mg/dl)	SCR (mg/dl)	Na (mEq/L)	K (mEq/L)	Serum Osmolality(mosm/kg)	PH	REQUIREMENT OF INSULIN(U)	DKA (Y/N)	HHS(Y/N)	ASSOCIATED COMPLICATIONS OF DIABETES MELLITUS	OUTCOME
1	SRINIVAS	848371	29	ALTERED SENSORIUM	MALE	1	10YEARS	PNEUMONIA	NO	YES	NO	534	11.7	38	1.1	135	3.5	314	7.11	71	YES	NO	RETINOPATHY	SURVIVED
2	VANITHA	899913	45	VOMITIG;NAUSEA;DEHYDRATION	FEMALE	2	5YEARS	URINARY TRACT INFECTION	YES	NO	NO	HIGH	9.4	33	0.9	130	4	310	7.2	82	YES	NO	RETINOPATHY	SURVIVED
3	MOHAN	936711	53	VOMITIN;TACHYCARDIA	MALE	2	2YEARS	DIABETIC FOOT	YES	NO	NO	500	10.7	22	0.6	136	4.6	312	7.14	48	YES	NO	NEPHROPATHY	SURVIVED
4	MANJULA	935627	24	ACIDOTIC BREATHING	FEMALE	1	4YEARS	PNEUMONIA	NO	YES	NO	490	9.8	33	0.8	140	4	318	7.22	52	YES	NO	NO	SURVIVED
5	FAZULA	937762	55	ACIDOTIC BREATHING	FEMALE	2	12YEARS	DIABETIC FOOT	YES	NO	YES	348	10.4	63	1.2	125	5.5	318	7.11	38	YES	NO	RETINOPATHY	SURVIVED
6	DEVA REDDY	935286	50	NAUSEA;VOMITING	MALE	2	2DAYS	PNEUMONIA	NO	NO	NO	HIGH	10	68	0.6	154	3.3	342	7.38	91	NO	YES	NEPHROPATHY;RETINOPATHY	SURVIVED
7	CHANDRA REDDY	917497	70	VOMITING;DEHYDRATION	MALE	2	22YEARS	SEPSIS	NO	YES	YES	HIGH	12	30	1.1	130	5.4	346	7.38	68	NO	YES	NEUROPATHY;CAD	SURVIVED
8	VARADAPPA	931230	52	ALTERED SENSORIUM	MALE	2	2YEARS	PNEUMONIA	YES	NO	YES	HIGH	11	34	0.8	122	3.1	351	7.42	66	NO	YES	RETINOPATHY	SURVIVED
9	SUJI	930240	48	NAUSEA;VOMITING	MALE	2	4YEARS	URINARY TRACT INFECTION	YES	NO	NO	504	10.7	64	0.9	158	6	310	7.14	58	YES	NO	NEPHROPATHY	SURVIVED
10	SUBAN SABI	931675	68	NAUSEA;VOMITING;HYPOTENSION	MALE	2	14YEARS	SEPSIS	NO	YES	YES	HIGH	10.8	33	1.2	123	3	338	7.4	71	NO	YES	CAD;RETINOPATHY	DEATH
11	MEGHANA	932518	36	ALTERED SENSORIUM;HYPOTENSION	FEMALE	1	12YEARS	PNEUMONIA	NO	YES	NO	HIGH	11.4	44	0.8	144	2.4	345	7.44	66	NO	YES	CVA;RETINOPATHY	SURVIVED
12	SUREAH BABU	833943	38	ABDOMINALPAIN;VOMITING	MALE	1	11YEARS	URINARY TRACT INFECTION	NO	YES	NO	HIGH	12	34	1	150	3	352	7.36	80	NO	YES	NO	SURVIVED
13	SYED ABDUL	929144	75	NAUSEA;VOMITING;HYPOTENSION	MALE	2	24YEARS	DIABETIC FOOT	YES	YES	YES	422	12.4	62	0.6	124	2.6	310	7.11	46	YES	NO	CVA;NEPHROPATHY	DEATH
14	NARAYANA REDDY	937582	65	NAUSEA;VOMITING;ABDOMINAL PAIN	MALE	2	18YEARS	DIABETIC FOOT	NO	YES	YES	HIGH	11.4	32	0.4	152	2.4	360	7.4	66	NO	YES	RETINOPATHY;CAD	SURVIVED
15	RATHNAMMA	901649	48	VOMITING;NAUSEA	FEMALE	2	11YEARS	PNEUMONIA	YES	NO	YES	HIGH	12.1	40	0.8	124	5.4	343	7.38	92	NO	YES	RETINOPATHY	SURVIVED
16	SHAHANAZ BEGUM	893914	33	ACIDOTIC BREATHING	FAMALE	1	12YEARS	URINARY TRACT INFECTION	NO	YES	NO	424	10.6	28	0.5	126	2.4	308	7.1	61	YES	NO	NO	SURVIVED
17	NARAYANA SWAMY	881868	58	ABDOMINAL PAIN;HYPOTENSION	MALE	2	4YEARS	PNEUMONIA	YES	NO	YES	520	10.1	33	0.8	134	6	312	7.11	72	YES	NO	RETINOPATHY;CAD	SURVIVED
18	VISHNU	947891	30	NAUSEA;VOMITING	MALE	1	10YEARS	PNEUMONIA	NO	YES	NO	HIGH	9.8	38	1.1	128	3.4	346	7.39	98	NO	YES	NEPHROPATHY	SURVIVED
19	MUNIRATHNAMMA	884912	70	ACIDOTIC BREATHING	FEMALE	2	7YEARS	DIABETIC FOOT	YES	YES	YES	348	11.1	34	0.8	134	2.4	316	7.2	43	YES	NO	RETINOPATHY;NEPHROPATHY	SURVIVED
20	LAKSHMIDEVAMMA	946963	52	NAUSEA;VOMITING	FEMALE	2	12YEARS	URINARY TRACT INFECTION	NO	NO	NO	HIGH	12.9	33	0.6	126	3.3	348	7.37	88	NO	YES	RETINOPATHY	SURVIVED
21	HANUMANTHA RAJU	980403	68	TACHYCARDIA;HYPOTENSION	MALE	2	11YEARS	PNEUMONIA	YES	YES	NO	HIGH	13	24	0.6	124	5.8	352	7.38	108	NO	YES	CAD	SURVIVED
22	BHADRAMMA	974007	50	NAUSEA;VOMITING	FEMALE	2	2YEARS	DIABETIC FOOT	NO	YES	YES	442	9.9	18	0.7	134	2.6	312	7.18	62	YES	NO	RETINOPATHY	SURVIVED
23	MUNIYAPPA	907648	68	ABDOMINAL PAIN	MALE	2	12YEARS	PNEUMONIA	NO	YES	YES	HIGH	12.8	71	1.4	124	4	348	7.43	104	NO	YES	NEPHROPATHY	SURVIVED
24	SUJATHAMMA	963705	35	PAIN ABDOMEN;VOMITING	FEMALE	1	10YEARS	PNEUMONIA	NO	YES	NO	400	11.1	34	0.5	130	3.3	308	7.15	48	YES	NO	RETINOPATHY	SURVIVED
25	NAGARAJ	972306	55	HYPOTENSION;TACHYCARDIA	MALE	2	15YEARS	SEPSIS	YES	NO	YES	HIGH	13	28	1	124	2.6	338	7.38	114	NO	YES	CAD;RETINOPATHY	DEATH
26	SRINIVAS	974609	24	ACIDOTIC BREATHING	MALE	1	8YEARS	PNEUMONIA	NO	YES	NO	441	12	22	0.4	134	5.6	314	7.12	58	YES	NO	NO	SURVIVED
27	SEENAPPA	977137	80	TACHYCARDIA;HYPOTENSION	MALE	2	22YEARS	SEPSIS	YES	YES	YES	HIGH	12	44	1.2	126	3.1	342	7.4	124	NO	YES	CAD;NEPHROPATH	SURVIVED
28	KEMPAMMA	973051	60	PAIN ABDOMEN;VOMITING	FEMALE	2	14YEARS	DIABETIC FOOT	YES	YES	YES	HIGH	11	34	1	134	3.4	346	7.38	112	NO	YES	RETINOPATHY	SURVIVED
29	SAVITHRAMMA	978181	77	VOMITING	FEMALE	2	17YEARS	DIABETIC FOOT	YES	YES	YES	HIGH	14	74	0.9	126	5.6	348	7.42	128	NO	YES	NEPHROPATHY	SURVIVED
30	BASHEER	962196	60	NAUSEA;VOMITING	MALE	2	12YEARS	PNEUMONIA	NO	NO	YES	424	13	32	0.6	133	3.3	320	7.12	68	YES	NO	NEUROPATHY;CAD	SURVIVED
31	SATHYA NARAYANA	947048	79	NAUSEA;VOMITING	MALE	2	24YEARS	SEPSIS	NO	YES	YES	HIGH	12	34	0.4	126	2.4	360	7.38	120	NO	YES	CVA;RETINOPATHY	SURVIVED
32	NARAYANAPPA	965745	75	ACIDOTIC BREATHING	MALE	2	18YEARS	DIABETIC FOOT	NO	NO	YES	HIGH	14	38	0.6	138	3.5	350	7.44	114	NO	YES	CVA;CAD	SURVIVED
33	SURESH	974321	24	VOMITING	MALE	1	11YEARS	PNEUMONIA	NO	YES	NO	454	13	36	0.8	128	3	312	7.11	48	YES	NO	NO	SURVIVED
34	SAROJA	962183	58	ABDOMINAL PAIN	FEMALE	2	13YEARS	DIABETIC FOOT	YES	NO	YES	423	12	34	0.6	136	2.3	313	7.14	54	YES	NO	RETINOPATHY;NEUROPATHYY	SURVIVED
35	NARAYANAPPA	972301	74	VOMITING	MALE	2	21YEARS	SEPSIS	YES	NO	YES	HIGH	13	33	0.8	134	6.1	343	7.46	122	NO	YES	CAD	SURVIVED
36	SAVITHRI	980504	60	ABDOMINAL PAIN;VOMITING	FEMALE	2	11YEARS	URINARY TRACT INFECTION	YES	YES	YES	HIGH	11	32	0.1	130	5	351	7.38	116	NO	YES	NO	SURVIVED
37	MANJU	991014	71	NAUSEA;VOMITING	MALE	2	14YEARS	DIABETIC FOOT	YES	YES	NO	HIGH	12	52	1	124	4	348	7.41	128	NO	YES	NEPHROPATHY	SURVIVED
38	BADRI	951342	30	ALTERED SENSORIUM	MALE	1	10YEARS	PNEUMONIA	NO	YES	NO	441	11	53	1.1	120	3.6	310	7.14	74	YES	NO	NO	SURVIVED
39	RATHNAMMA	961432	32	ALTERED SENSORIUM	FEMALE	1	6YEARS	URINARY TRACT INFECTION	NO	YES	NO	400	12	48	1.2	130	4	320	7.11	78	YES	NO	NO	SURVIVED
40	KARTHIK	921342	71	ABDOMINAL PAIN	MALE	2	20YEARS	SEPSIS	YES	YES	YES	HIGH	13	54	0.8	124	3.8	342	7.44	126	NO	YES	CAD	SURVIVED
41	BASHA	961234	56	VOMITING	MALE	2	13YEARS	DIABETIC FOOT	YES	NO	YES	HIGH	12	48	1	155	4	348	7.11	118	NO	YES	RETINOPATHY	SURVIVED
42	MAHESH	991432	56	DEHYDRATION	MALE	2	10YEARS	PERIANAL ABSCESS	NO	YES	NO	HIGH	13.1	55	1.2	126	3.8	350	7.42	124	NO	YES	RETINOPATHY	SURVIVED
43	KIRANMAI	943124	30	ACIDOTIC BREATHING	FEMALE	1	13YEARS	DIABETIC FOOT	NO	YES	NO	432	13	47	1	124	3.4	311	7.11	58	YES	NO	RETINOPATHY	SURVIVED
44	SANTOSH	991561	88	NAUSEA;VOMITING	MALE	2	25YEARS	SEPSIS	YES	YES	YES	HIGH	12	58	0.8	156	3.3	348	7.42	116	NO	YES	RETINOPATHY	SURVIVED
45	RAMA	921432	26	NAUSEA;VOMITING	FEMALE	1	7YEARS	PNEUMONIA	NO	YES	NO	431	13	30	0.5	130	3	311	7.12	61	YES	NO	NO	SURVIVED

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46	SANGEETHA	919204	32	ACIDOTIC BREATHING	FEMALE	1	9YEARS	SEPSIS	NO	YES	NO	461	12	34	0.8	126	6	308	7.2	56	YES	NO	NO	SURVIVED
47	NARAYANA SWAMY	941253	74	ALTERED SENSORIUM	MALE	2	18YEARS	DIABETIC FOOT	YES	YES	YES	HIGH	13.8	28	1	158	5.8	346	7.38	118	NO	YES	NEUROPATHY	SURVIVED
48	NANDEESH	973465	59	ALTERED SENSORIUM	MALE	2	20YEARS	URINARY TRACT INFECTION	YES	YES	YES	HIGH	13	38	0.6	130	5.5	348	7.41	120	NO	YES	CAD	SURVIVED
49	ANAND	978123	82	NAUSEA;VOMITING	MALE	2	26YEARS	DIABETIC FOOT	YES	YES	YES	HIGH	14	40	0.8	137	5.4	350	7.36	101	NO	YES	CAD	SURVIVED
50	SUBASH	946331	32	ACIDOTIC BREATHING	MALE	1	10YEARS	SEPSIS	NO	YES	NO	468	13.6	35	0.6	129	3	312	7.11	44	YES	NO	NO	SURVIVED