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PREDICTING AND PRECIPITATING FACTORS OF DIABETIC KETOACIDOSIS AMONG ADULT IRAQ

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ABSTRACT

Background: Diabetic ketoacidosis (DKA) is a common complication among adult with diabetes mellitus (DM), accounting for 14% to 31% of all diabetes-related hospital admissions; the risk of DKA in established type 1 diabetes mellitus (TIDM) is 1–10% per patient per year. ***Objective:*** The purpose of this work was to determine frequency of the predictors and the precipitating factors of DKA resulting in admission to hospital or emergency departments in adult Central Teaching Hospital in Iraq. ***Design*****:** case control study. ***Subjects and Methods*****:** During June thru November 2014, a sample of 27 Children with diabetic ketoacidosis (DKA) (11 males and 16 females; between 16 and 22years of age) and 28 adult with type 1 diabetes mellitus (T1DM), as a control group (14 males and 14 females; between 19.years and 21years of age) admitted to the adult Central Teaching Hospital in Iraq were studied. Data regarding history, full physical examination, and laboratory investigations (presence of glucose and/or ketones in urine, serum potassium (m.Eq/l), blood bicarbonate (mmol/L), venous pH, blood glucose (mmol/100ml), and the treatment given were recorded. Analysis was performed by using SPSS version 16, and all statistical analysis was done at 95% confidence level. Statistical significance was accepted when $p \leq 0.05$. ***Results:*** Most of my patients were 18-22 years old in both cases and control groups 12(44.4%) and 10 (35.7%) respectively. The frequency of DKA was significantly higher in girls than in boys 16(59.3) vs. 11 (40.7%); $p < 0.05$), more than two thirds of patients with DKA 19 (70.4%) were from families with lower income as compared to16 (57.1%) of the control group, In 15 (55.6%) it was the first time they were discovered to be diabetic. Seven (58.3%) of known diabetic patients had history of previous attacks of DKA and previous attacks of hypoglycemia were encountered in 10 (83.3%) of cases. The most common precipitating causes of DKA was infection, which occurred before 12 (44.4%) of the episodes, no identifiable cause for the

episode was encountered in 7 (25.9%) of cases, missing the usual dose of insulin, and stress were identified in 3 (11.1%) for each, and increased food intake was documented as a precipitating factors in 2 (7.4%) of cases. ***Conclusions*:** Infection, increased food intake, missing the usual dose of insulin, and stressful conditions are the main precipitating factors for DKA; female gender, low family income, history of previous attack of either DKA or hypoglycemia are predicting factors. ***Recommendations*** it is also recommended that the education about how to care for a adult with diabetes must be provided to the entire family unit in order to protect him from the possible episode of DKA.

KEYWORDS: Diabetic ketoacidosis (DKA), diabetes mellitus (DM).

INTRODUCTION

Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia due to defective insulin secretion, insulin action or both, this chronic hyperglycemia is associated with significant long term complications including damage, dysfunction and failure of various organs especially the kidneys, eyes and nerves and is associated with markedly increased risk of cardiovascular morbidity and mortality.[1] The abnormalities in carbohydrate, fat, and protein metabolism that are found in diabetes are due to the deficient action of insulin on target tissues; If ketones are present in the blood or urine, treatment is urgent because ketoacidosis can evolve rapidly.[2]

Type 1 diabetes mellitus (TIDM) (sometimes called insulin-dependent or childhood-onset diabetes) occurs when the pancreas does not produce enough insulin, a hormone that regulates blood sugar. The cause is not known, but it is thought to be the result of a combination of genetic and environmental factors. Type2 diabetes mellitus (T2DM) (sometimes called non-insulin-dependent or adult-onset diabetes) happens when the body cannot effectively use the insulin it produces. Often preventable, it can result from excess body weight and physical inactivity, and sometimes, a genetic predisposition.[3]

Type1 diabetes is the most common form of diabetes in most part of the world,[4] and many countries are documenting higher numbers of newly diagnosed cases of type1 diabetes, particularly in younger children. Interestingly, some disease patterns among children resemble infectious disease epidemics. Currently, there is no known way to prevent TIDM.[3]

Recently, T2DM has increasingly been reported in children and adolescents, so much so that in some parts of the world type2 diabetes has become the main type of diabetes in children. The global rise of childhood obesity and physical inactivity is widely speculated to play a crucial.[3]

The frequency of diabetes is rising around the world, and studies are showing children are at increasing risk of developing the disease. More than 180 million people worldwide have the illness, a number likely to more than double by 2030 without intervention, according to estimates released in 2004.[3]

Available data from many countries of the Eastern Mediterranean Region (EMR) indicate that diabetes mellitus has become a problem of great magnitude and a major public health concern. Studies have demonstrated that, in some countries, diabetes affects up to 10% of the population aged 20 years and older. This rate may be doubled if those with impaired glucose tolerance (IGT) are also included.[5]

According to the World Health Organization (WHO) the prevalence of DM in Iraq is 6.1% for both males and females.[6]

Diagnosis of DM

The diagnosis of type 1 diabetes in adult is usually straightforward and requires little or no specialized testing. Most adult with TIDM present with a several-week history of polyuria, polydipsia, polyphagia, and weight loss, with hyperglycemia, glycosuria, ketonemia, and ketonuria. Glycosuria alone, especially without ketonuria, may be caused by a low renal glucose threshold. Thus, an elevated blood glucose concentration must be documented to diagnose diabetes. Similarly, the incidental discovery of hyperglycemia in the absence of classic symptoms does not necessarily indicate new onset diabetes, especially in young adult with acute illness.[7]

Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is the most common hyperglycemic emergency in patients with DM, and it is the leading cause of morbidity and mortality in adult with T1DM.[8,9]

Diabetic ketoacidosis most often occurs in patients with T1DM, it is uncommon in T2DM, as there is some degree of endogenous insulin present in these patients,[10] but it has been reported to occur in T2DM,[11] and it has been reported that patients with T2DM are

susceptible to DKA under stressful conditions, such as trauma, surgery, or infections Non-compliance to treatment and infection were reported to be the most common precipitating factors of DKA.[12,13]

Diabetic ketoacidosis is a common complication among adult with diabetes, accounting for 14% to 31 % of all diabetes-related hospital admissions,[14] and it is reported to be responsible for more than 100 000 hospital admissions per year in the US, and accounts for 4-9% of all hospital discharge summaries among patients with diabetes.[15]

Metabolic control may deteriorate during infections, stressful conditions and other intercurrent illnesses. Both the health care team and the person with diabetes should take note of this fact and take action to avoid complications, Actions to be taken include the following:

1. More frequent monitoring of urine and blood glucose.
2. Monitoring of urinary ketones.
3. Recognition of symptoms and signs of ketoacidosis (vomiting and other gastrointestinal symptoms, dehydration, etc.) and early referral to a specialist.[5]

Diabetic ketoacidosis remains a potentially lethal condition with mortality as high as 10 to15%; however, at least 50% of cases are avoidable. Many new patients with TIDM present with ketoacidosis, so early recognition and diagnosis are clearly of importance,[6] and The number of episodes DKA is a significant outcome measure for diabetes care.[16]

Pathophysiology of Diabetic Ketoacidosis

Diabetic ketoacidosis results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counter regulatory hormones: catecholamines, glucagon, cortisol, and growth hormone,[17] this leads to increased glucose production by the liver and kidney and impaired peripheral glucose utilization with resultant hyperglycaemia, and hyperosmolality. Increased lipolysis, with ketone body (beta-hydroxybutyrate, acetoacetate) production causes ketonaemia and metabolic acidosis. Hyperglycaemia and acidosis result in osmotic diuresis, dehydration, and obligate loss of electrolytes. The detailed pathophysiology of DKA is shown in figure 1.[18]

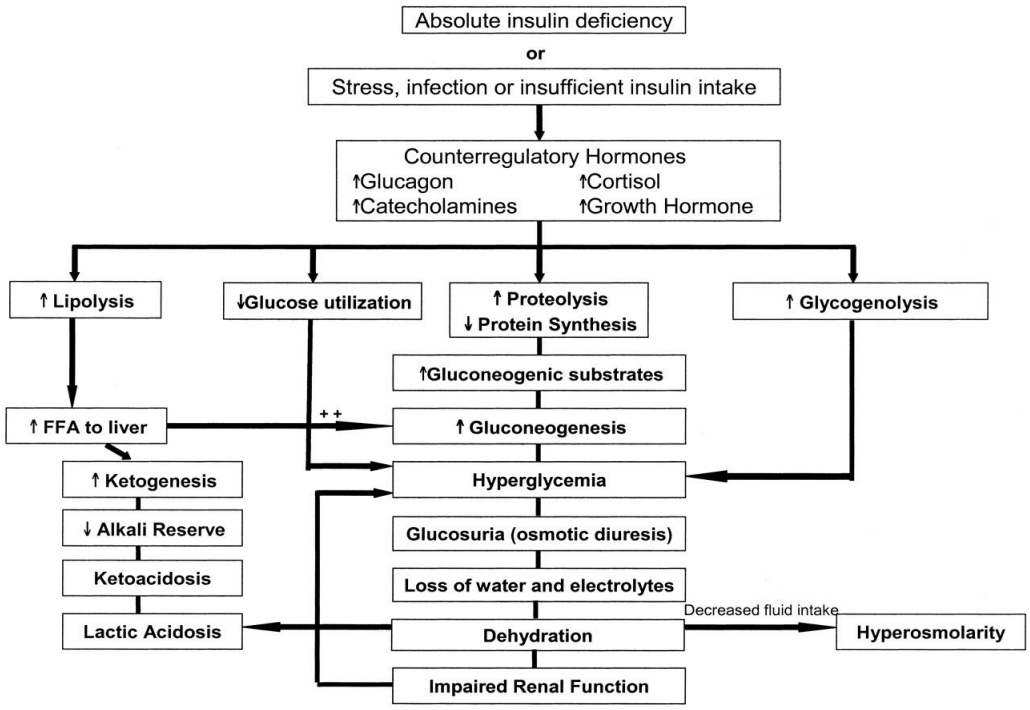

Figure 1: Pathophysiology of DKA.

The biochemical criteria for the diagnosis of DKA According to the international society for pediatric and adolescence diabetes (ISPAD), includes hyperglycaemia (blood glucose .11 mmol/l (200 mg/dl)) with a venous PH, 7.3 and/or bicarbonate, 15 mmol/l. There is associated glycosuria, ketonuria, and ketonaemia. Rarely, young or partially treated adult as well as pregnant adolescents may present with near normal glucose values (‘‘euglycaemic ketoacidosis’’).[8] Neu A.etal and Rewers A (2008) defined DKA as venous blood glucose > 250 mg/dL pH < 7.30 or bicarbonate < 15 mmol/L and ketonuria.

DKA is generally categorized by the severity of the acidosis; varying from mild (venous PH, 7.30, bicarbonate concentration, 15 mmol/l), to moderate (pH, 7.2, bicarbonate, 10), to severe (pH, 7.1, bicarbonate, 5).[8,18] The arbitrarily classification of Alemzadeh R and Wyatt DT (2007) into similar categories are is shown in table 1.[19]

Table 1: Classification of DKA.

DKA Category	HCO3 (venous) meq/l	PH (venous)	Clinical
Normal	20-28	7.35-7.45	No change
Mild	16-20	7.25-7.35	Oriented, alert but fatigue
Moderate	10-15	7.15-7.25	Kussmaul respirations Oriented but sleepy, arousable
Sever	<10	<7.15	Kussmaul or depressed respirations Sleepy or depressed sensorium to coma

*(Nelson Textbook of Pediatrics Saunders; 18th editions (2007)

Causes of ketoacidosis

Ketones mean that the body is burning fat to get energy. Moderate or large amounts of ketones in urine are dangerous. They upset the chemical balance of the blood. there are three basic reasons for moderate or large amounts of ketones:

1. Not getting enough insulin. May be because that not enough insulin is injected; or the body could need more insulin than usual because of illness. If there is not enough insulin, the body begins to break down body fat for energy.
2. Not enough food. When people are sick, they often do not feel like eating. Then, high ketones may result. High ketones may also occur when someone misses a meal.
3. An insulin reaction (low blood glucose). When blood glucose levels fall too low, the body must use fat to get energy. If testing shows high ketones in the morning, the person may have had an insulin reaction while asleep.[20]

Frequency of DKA and Precipitating Factors

Internationally the exact incidence is unknown.[21]

A. At disease onset

There is wide geographic variation in the frequency of DKA at onset of diabetes; Reported frequencies range between 15% and 67% in Europe and North America and may be more common in developing countries).[8] In Canada and Europe, hospitalisation rates for DKA in established and new patients with TIDM have remained stable at about 10 per 100 000 children over the past 20 years, but severity may be decreasing. A recent survey throughout the U.S. showed that the rate of DKA is ~25% at the time of diagnosis.[18]

DKA at diagnosis is more common in younger adult (<18 years of age) and in adutl whose families do not have ready access to medical care for social or economic reasons. Lower income and lower parental educational achievement were associated with higher risk of DKA. Thus, younger and poorer adult are disproportionately affected.[18] DKA at onset of TIDM is more common in younger adult without a first degree relative with TIDM, and those from families of lower socioeconomic status.

High dose glucocorticoids, atypical antipsychotics, diazoxide, and some immunosuppressive drugs have been reported to precipitate DKA in individuals not previously diagnosed with TIDM.[8]

B. In adult with established TIDM

The risk of DKA in adult with established TIDM is 1–10 per 100 person-years; The risk is increased in adult with poor metabolic control or had previous episodes of DKA; peripubertal and adolescent girls; adult with psychiatric disorders, including those with eating disorders; and those with difficult family circumstances, including lower socioeconomic status and children with limited access to medical services.[18]

Insulin omission, either inadvertently or deliberately, is the cause in most cases. There is usually an important psychosocial reason for omitting insulin. Inappropriate interruption of insulin pump therapy for any reason rapidly leads to insulin deficiency and leads to DKA (as only rapid- or short-acting insulin is used in pumps, interruption of insulin delivery.[18,20]

An intercurrent infection is seldom the cause when the patient/family is properly educated in diabetes management.[18] otherwise, the flu, a cold, or other infections may sometimes bring on ketoacidosis.[20]

Adult whose insulin is administered by a responsible adult rarely have episodes of DKA and 75% of episodes of DKA beyond diagnosis are probably associated with insulin omission or treatment error. The remainders are due to inadequate insulin therapy during intercurrent illness.[8]

Clinical Presentation

According to the American diabetes association ketoacidosis usually develops slowly. But when vomiting occurs, this life-threatening condition can develop in a few hours.[20] The first symptoms are

- Thirst or a very dry mouth
- Frequent urination
- High blood glucose levels
- High levels of ketones in the urine

  Next, other symptoms appear
- Constantly feeling tired
- Dry or flushed skin
- Nausea, vomiting, or abdominal pain
- A hard time of breathing (short, deep breaths)
- Fruity odor on breath

- A hard time for paying attention, or confusion

Management of DKA

1. General Issues

adult with ketosis and hyperglycemia without vomiting or severe dehydration can be managed at home or in an outpatient health care setting (eg, emergency ward or units with similar facilities), but the level of care needs to be reevaluated frequently and supervised by an experienced diabetes team.[14,22]

A specialist/consultant pediatrician with training and expertise in the management of DKA should direct inpatient management. The also adult should be cared for in a unit that has experienced nursing staff trained in monitoring and management, clear written guidelines, and access to laboratories for frequent evaluation of biochemical variables.[8]

adult with signs of severe DKA (long duration of symptoms, compromised circulation, or depressed level of consciousness) or those who are at increased risk for cerebral edema (including <18 years of age and new onset) should be considered immediately for treatment in an intensive care unit (pediatric, if available) or a adult ward specializing in diabetes care with equivalent resources and supervision.[23] If transfer by ambulance to another unit is required, caution should be exercised in the use of sedatives and antiemetic.[8]

2. Monitoring

There should be documentation of hour-by-hour clinical observations, IV and oral medication, fluids, and laboratory results during the entire treatment period. Monitoring should include

1. Hourly heart rate, respiratory rate, and blood pressure.
2. Hourly (or more frequent), accurate fluid input and output (when there is impaired level of consciousness, urinary catheterization may be necessary).
3. In severe DKA, electrocardiogram monitoring may be helpful to assess T-waves for evidence of hyperkalemia/hypokalemia.
4. Capillary blood glucose should be monitored hourly (but must be cross-checked against laboratory venous glucose, because capillary methods may be inaccurate in the presence of poor peripheral circulation and acidosis).
5. Laboratory tests: electrolytes, urea, hematocrit, blood glucose, and blood gases should be repeated every 2 to 4 hours. (However, electrolytes should be monitored hourly as

clinically indicated in the more-severe cases.) An elevated white blood cell count may be due to stress and cannot be taken as a sign of infection.

6. Hourly or more-frequent neurologic observations for warning signs and symptoms of cerebral edema (Headache, Inappropriate slowing of heart rate,Recurrence of vomiting, Change in neurologic status (restlessness, irritability, increased drowsiness, or incontinence), or specific neurologic signs (eg, cranial nerve palsies or pupillary response), Rising blood pressure, Decreased oxygen saturation)

Those monitoring should be instructed to alert the physician of any of these manifestations, because it may be difficult to clinically discriminate cerebral edema from other causes of altered mental status.[8]

3. Fluids and Salt

Water and salt deficits must be replaced. IV or oral fluids that may have been given before the child presents for treatment and prior to assessment should be factored into calculation of deficit and repair.

- Initial IV fluid administration and, if needed, volume expansion should begin immediately with an isotonic solution (0.9% saline or balanced salt solutions such as Ringer's lactate). The volume and rate of administration depend on circulatory status, and where it is clinically indicated, the volume is typically 10 to 20 ml/kg over 1 to 2 hours, repeated if necessary.
- Use crystalloid.
- Subsequent fluid management (deficit replacement) should be with 0.9% saline or a balanced salt solution such as Ringer's lactate (or acetate) for at least 4–6 h. Thereafter, deficit replacement should be with a solution that has a tonicity ≥0.45% saline with added potassium chloride, phosphate, or acetate. The rate of intravenous fluid should be calculated to rehydrate evenly over at least 48 h.
- In addition to clinical assessment of dehydration, calculation of effective osmolality may be valuable to guide fluid and electrolyte therapy.
- Because the severity of dehydration may be difficult to determine and can be overestimated, infuse fluid each day at a rate rarely in excess of 1.5 to 2 times the usual daily requirement based on age, weight, or body surface area. Urinary losses should not be added to the calculation of replacement fluids.[18]

The onset of dehydration is associated with a reduction in glomerular filtration rate (GFR), which results in decreased glucose and ketone clearance from the blood. Rehydration also lowers glucose levels by improving renal perfusion and enhancing renal excretion.[19]

The objectives of fluid and sodium replacement therapy in DKA are 1) restoration of circulating volume, 2) replacement of sodium and the extracellular fluid (ECF) and intracellular fluid (ICF) deficit of water, 3) restoration of GFR with enhanced clearance of glucose and ketones from the blood, and 4) avoidance of cerebral edema.

4. Insulin

Although rehydration alone causes some decrease in blood glucose concentration, insulin therapy is essential to normalize the blood glucose concentration and suppress lipolysis and ketogenesis. Although different routes (subcutaneous, intramuscular, and IV) and doses have been used, extensive evidence indicates that "low-dose" IV insulin administration should be the standard of care.

Physiologic studies indicate that IV insulin at a dose of 0.1 unit/kg per hour, which achieves steady-state plasma insulin levels of ~100 to 200 µU/mL within 60 minutes, is effective. Such plasma insulin levels are able to offset insulin resistance and, in most circumstances, inhibit lipolysis and ketogenesis, exerting maximal or near-maximal effects on suppression of glucose production and stimulated peripheral glucose uptake. The resolution of acidemia invariably takes longer than normalization of blood glucose concentrations.

- The dose of insulin should remain at least 0.1 U/kg per hour at least until resolution of ketoacidosis (pH: >7..3; HCO3: >15 mmol/L and/or closure of anion gap). To prevent an unduly rapid decrease in plasma glucose concentration and possible development of hypoglycemia, glucose should be added to the IV fluid when the plasma glucose falls to 14 to 17mmol/L (250–300mg/dL).
- There may be circumstances in which the insulin dose may be safely reduced earlier, but the criteria have not been defined.
- If biochemical parameters of ketoacidosis (pH and anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin (eg, infection, errors in insulin preparation, or adhesion of insulin to tubing with very dilute solutions).

- There is evidence that an IV bolus of insulin is not necessary. However, a bolus may be used at the start of insulin therapy, particularly if insulin treatment has been delayed.
- In unusual circumstances in which IV administration is not possible, the intramuscular or subcutaneous route of insulin administration has been used effectively**.** However, poor perfusion will impair absorption of insulin.

5. Potassium

Serum potassium levels at the time of presentation may be normal, increased or decreased: Hypokalemia at presentation may be related to prolonged duration of disease, whereas hyperkalemia primarily results from reduced renal function.[25] Administration of insulin and the correction of acidosis will drive potassium back into the cells, decreasing serum levels. Therefore the following points should be taken into consideration in the management:

- Potassium replacement is required.
- Replacement therapy should be based on serum potassium measurements.
- Start potassium replacement immediately if the patient is hypokalemic; otherwise, start potassium concurrent with starting insulin therapy. If the patient is hyperkalemic, defer potassium until urine output is documented.
- Starting potassium concentration in the infusate should be 40mmol/L, and potassium replacement should continue throughout IV fluid therapy.

6. Acidosis

Even severe acidosis is reversible by fluid and insulin replacement. Administration of insulin stops further ketoacid synthesis and allows excess ketoacids to be metabolized. The metabolism of keto-anion results in the regeneration of bicarbonate (HCO_3^-) and spontaneous correction of acidemia. Also, treatment of hypovolemia will improve decreased tissue perfusion and renal function, thus increasing the excretion of organic acids and reversing any lactic acidosis, which may account for 25% of the acidemia.

The indications for bicarbonate therapy in DKA are unclear. Several controlled trials of sodium bicarbonate in small numbers of children and adults have been unable to demonstrate clinical benefit or any important difference in the rate of rise in the plasma bicarbonate concentration.[26,27,28]

These findings, however, do not address the issue that there may be selected patients who may benefit from cautious alkali therapy, including those with severe acidemia (arterial pH:

<6.9) in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion and patients with potentially life-threatening hyperkalemia.[9]

Treatment of Cerebral Edema

Treatment should be initiated as soon as the condition is suspected. The rate of fluid administration should be reduced. Although mannitol has been shown to have possible beneficial effects in case reports,[29] there has been no definite beneficial or detrimental effect in retrospective epidemiologic studies.[30]

The response may be altered by timing of administration, delayed administration being less effective. IV mannitol should be given (0.25–1.0 g/kg over 20 minutes) in patients with signs of cerebral edema before impending respiratory failure. Repeat in 2 hours if there is no initial response. Hypertonic saline (3%), 5 to 10 mL/kg over 30 minutes, may be an alternative to mannitol.[31]

Intubation and ventilation may be necessary. However, aggressive hyperventilation has been associated with poor outcome in one retrospective study of DKA-related cerebral edema.[30] There are no data regarding glucocorticoid use in DKA-related cerebral edema.

Morbidity and Mortality of DKA in adult

With current medical therapy, DKA has a 2-5% mortality rate. Mortality results from the precipitating underlying cause, which is primarily cerebral edema. Cerebral edema occurs in 0.3-1% of all episodes of DKA.[21]

Reported mortality rates from DKA in national population based studies are reasonably constant: 0.15% (USA), 0.18% - 0.25% (Canada), and 0.31% (UK). In places with less developed medical facilities, the risk of dying from DKA is greater, and children may die before receiving treatment, Cerebral edema accounts for between 57% and 87% of all DKA deaths.[8]

Other possible causes of mortality and morbidity include hypokalemia, hyperkalemia, hypoglycemia, other central nervous system (CNS) complications, hematoma ,thrombosis, sepsis, infections (including rhinocerebral mucormycosis) aspiration pneumonia, pulmonary edema adult respiratory distress syndrome pneumomediastinum and subcutaneous emphysema and rhabdomyolysis Late sequelae relate to cerebral edema and other CNS

complications including hypothalamopituitary insufficiency, isolated growth hormone deficiency, and combined growth hormone and thyroid-stimulating hormone deficiency.[8]

Prevention of Recurrent DKA

Because of the significant mortality and morbidity associated with DKA, prevention is of paramount importance, There is agreement that prevention of DKA and reduction of its incidence should be a goal in managing children with diabetes.[9] and it has been reported that management of an episode of DKA is not complete until its cause has been identified and an attempt made to treat it and all cases of recurrent DKA are preventable.[32]

Although diabetic ketoacidosis should, theoretically, be largely preventable in patients with established diabetes, a recent report from a major US childhood diabetes center showed that adult with type 1 diabetes remain at high risk for diabetic ketoacidosis, with an incidence of 8 per 100 patient-years.[33]

The prevention of DKA by early recognition and treatment of ketonuria, in either the newly or previously diagnosed patients, is the most effective method of reducing the morbidity and mortality. Treatment of ketonuria in the patient previously diagnosed with diabetes usually starts and is completed in the home if it is detected early. Early treatment at home depends on adequate education of the family as well as on compliance. An educational manual and videotape are used for initial education as well as for intermittent reinforcement.[14]

Although infections are no more common in diabetic children than in non diabetic ones, they can often disrupt glucose control and may precipitate DKA. In addition, the diabetic adult is at increased risk of dehydration if hyperglycemia causes an osmotic diuresis or if ketosis causes emesis. Counter-regulatory hormones associated with stress blunt insulin action and elevate glucose levels.[19]

An educational program should include sick-day management instructions (i.e. for any illness that alters routine care), including the use of short-acting insulin, blood glucose and urinary ketone monitoring, and the use of a liquid diet containing carbohydrates and salt. Patients should not discontinue insulin therapy when they are ill, and they should contact their physician early in the course of illness. Indications for hospitalization include greater than 5 % loss of body weight, respiration rate of greater than 35 per minute, intractable elevation of

blood glucose concentrations, change in mental status, uncontrolled fever and unresolved nausea and vomiting.[34]

The prevention program for DKA in diabetic adult in the area of Parma, Italy was successful. The incidence of DKA was studied in newly diagnosed diabetic adult aged 16-18 years, 17 years after an information program on DKA was introduced to teachers, students, parents,. Information was provided by displaying a poster with a few practical messages in 177 primary and secondary public schools. The pediatricians working in the same area were given equipment for the measurement of glycosuria and blood glucose levels, as well as cards listing guidelines for the early diagnosis of diabetes, to be given to patients. A toll-free number was also provided. cumulative frequency of DKA in new-onset T1DM decreased from 78% during 1987-1991 to 12.5% during 1991-1997. None of the newly diagnosed diabetic children aged 6-14 years and from the Parma area were ever admitted to the hospital for DKA after 1992.[35]

1. Before Diagnosis

Earlier diagnosis through genetic and immunologic screening of high-risk children such as in the recent Diabetes Prevention Trial–Type 1 Diabetes Study Group (DPT-1) study decrease DKA incidence at diabetes onset.[8]

High levels of awareness related to the existence of other members of families with TIDM also reduce the risk of DKA. A school and physician awareness campaign, targeted at 16-22 year olds, reduced rates of DKA from 78% to almost 0% over a 6-year period.[35]

Increased public awareness of signs and symptoms of diabetes should lead to earlier diagnosis, particularly in children <18 years; checking urine or blood for glucose may prevent misdiagnosis

Although such strategies are intuitively obvious, programs to decrease DKA at onset need to be designed and evaluated in diverse populations and age groups.[8]

2. Beyond Diagnosis

Studies of the effects of comprehensive diabetes programs and telephone help lines report a reduction in the rates of DKA from 15–60 to 5–5.9/100 patient-years.[36]

In patients on continuous subcutaneous insulin pumps, episodes of DKA can be reduced with the introduction of educational algorithms. Therefore, it is likely that episodes of DKA after diagnosis could be reduced if all children with diabetes receive comprehensive diabetes health care and education and have access to a 24-hour diabetes telephone help line.

Multiple episodes of recurrent DKA are more problematic: In a recent United Kingdom study, 4.8% of patients accounted for 22.5% of all episodes over a 3-year period. Insulin omission has been identified as the major factor in most of these cases and may be confirmed by finding low free-insulin levels on admission.[9]

There is no evidence that mental health interventions alone can impact on the frequency of DKA in these children.[36,37] but insulin omission can be prevented by sequential schemes providing education, psychosocial evaluation, and treatment combined with adult supervision of insulin administration . When responsible adults administer insulin, a 10-fold reduction in episodes of DKA has been reported.[38]

Prevention of recurrent DKA remains a major challenge for diabetologists and involves detailed assessment of family psychodynamics plus responsibility for home monitoring and insulin administration by a mature adult. Sick day guidelines should be taught and reviewed frequently in an effort to decrease ketoacidosis and metabolic decompensation during episodes of intercurrent illness.[39]

DKA as an initial manifestation of T1DM may be less amendable to prevention except with an increased awareness by the lay and medical communities of the symptoms of diabetes and surveillance in high-risk populations potentially identified by family history or genetic susceptibility.[40]

Silverstein J et al (2005) summarized that prevention can be achieved through

1. Public awareness of the signs and symptoms of untreated diabetes.
2. Education of friends, roommates, and other caregivers about the signs and symptoms of early DKA.
3. Increased recognition that insulin omission due to psychological problems and lack of financial resources is the most common cause of DKA in patients with established diabetes.
4. Improved detection of families at risk.

5. Education about ketone monitoring.
6. 24-h telephone availability and encouragement to contact the healthcare team when blood glucose levels are high, when there is ketonuria or ketonemia, and especially during intercurrent illness.[7]

   Patient education and a team approach are effective ways of preventing or reducing the severity of future episodes. Increasing levels of awareness about the sick day rule among patients and health care providers should reduce repeated admissions.[41]

OBJECTIVE

This work was conducted to study the association of the different predicting and precipitating factors for the development of DKA admitted to the Central Teaching Hospital, Iraq.

PATIENTS AND METHODS

Design: A case control, hospital based study was conducted in the adult Central Teaching Hospital -Iraq during the period from June thru November 2014. All adult with DKA admitted to the hospital were studied (N=27) in addition to a control sample comprising the diabetic children admitted to the hospital for reasons other than DKA i.e. the control of their DM, (N=28) during the same period were studied.

Data collection

Approval of the study protocol and written informed consent for the study was obtained from the Authority of the hospital, and oral assent was also obtained from parents prior to data collection.

The preliminary version of the questionnaire was finalized for application after being pretested in a pilot study on 5 in patients with DKA; after which minor modifications were made to the original questionnaire by eliminating confusing items. The final analysis did not include the results of the pilot survey.

The 34 items, structured questionnaire (Appendix), includes items such as sex, age, residency, family income, family size, educational levels of parents, occupation of parents, whether the child is known to be diabetic, family history of DM, past history of previous attacks of DKA and/or hypoglycemia and they were questioned about the possible precipitating factors.

The information's were obtained from the companions; clarifications and basic orientation on the objectives of the study were given beforehand. Full physical examination performed and laboratory investigations including presence of glucose and/or ketones in urine, serum potassium (m.Eq/l), blood bicarbonate (mmol/L), venous pH, blood glucose (mmol/100ml). Treatment including insulin, fluid and electrolytes replacement and treatment of the cause of DKA (such as infection) was given as required. The patients were followed until discharge from the hospital.

Management

Immediate intravenous access and fluid and electrolytes replacement regimen were established in all 27 patients. All patients had their blood glucose documented on arrival; the biochemical profiles that were documented for the patients included blood PH, HCO3 (m.Eq/l), Serum potassium (m.Eq/l) together with the urine sample examination for the presence of glucose and ore ketones. The same investigations were applied to the 28 patients of the control group who were admitted for the control of their DM.

All patients were started on an intravenous insulin regimen with blood glucose monitoring at appropriate intervals; together with fluid and electrolyte replacement; all received potassium and antibiotics were given to those in whom intercurrent illness was identified prior to admission

Definitions of Variables

DKA was defined as venous blood glucose > 250 mg/dL pH < 7.30 or bicarbonate < 15 mmol/L and ketonuria, and it was categorized according to the Alemzadeh R and Wyatt DT categories (2009).[19]

Age was categorized in groups as < 5, 5 - 10, and >10 years.

After BMI was calculated, the BMI number is plotted on the CDC BMI-for-age growth charts (for either girls or boys) to obtain a percentile ranking [42]. BMI-for-age weight status categories and the corresponding percentiles are shown in table 2.

Table 2: BMI-for-age weight status categories and the corresponding percentiles.

Weight Status Category	Percentile Range
Underweight	Less than the 5th percentile
Healthy weight	5th percentile to less than the 85th percentile
Overweight	85th to less than the 95th percentile

Obese	Equal to or greater than the 95th percentile

From: CDC. About BMI for Children and Teens

Statistical analysis

Statistical analysis was performed by using SPSS version 16, and all was done at 95% confidence level. Statistical significance was accepted when $p \leq 0.05$.

There were a number of missing responses for some items of the questionnaire. But no questionnaire contained more than one missing response therefore they were considered satisfactory. A replacement-of-missing-value operation was undertaken for them, without affecting the data distribution or mean values. The SPSS "replace" function was used to replace the missing values by the means of all values.

Descriptive statistics including mean (± standard deviation) for continuous and proportion for categorical variables were computed for the demographic characteristics.

RESULTS

In total, the study subjects included 27 patients (11males and 16 females) who were admitted with confirmed DKA as cases and 28 patients (14 males and 14 females) with DM who were admitted to control their diabetes as control group; all were classified as having T1DM. There was no significant difference ($P > 0.05$) between the mean age of patients with DKA and those of the control group (9.16 ± 3.87 years (range between 11 months and 15 years), and 9.53 ± 4.03 years (range 2.1 - 15.6 years of age respectively). Table 3 illustrates the demographic characteristics of the study subjects.

Table 3: Demographic characteristics of the study groups.

Variable	Cases		Control	
	Frequency	**Percentage**	**Frequency**	**Percentage**
Gender				
Male	11	40.7	14	50.0
Female	16	59.3	14	50.0
Age group (years)				
< 18	3	11.1	4	14.3
18-22	12	44.4	10	35.7
> 22	12	44.4	14	50.0
Residency				
Urban	22	81.5	25	89.3
Rural	5	18.5	3	10.7
Family income (ID)				

< 300000	9	33.3	5	17.9
300000 – 600000	10	37.1	11	39.2
> 600000	8	29.6	12	42.9
Father education				
Postgraduate	5	18.5	1	3.6
University	2	7.4	6	21.4
Secondary	12	44.4	13	46.4
Primary	5	18.5	7	25.0
Less than primary	3	11.1	1	3.6
Mother education				
Postgraduate	2	7.4	-	-
University	1	3.7	1	3.6
Secondary	12	44.4	16	57.1
Primary	10	37.0	7	25.0
Less than primary	2	7.4	3	10.7
None	-	-	1	3.6
Family size				
Up to 5	9	33.3	12	42.9
6-10	14	51.9	14	50.0
More than 10	4	14.8	2	7.1
Total	27	100	28	100

Those aged 18 years and over suffered most frequently ($P < 0.001$) from both DKA and DM (88.8% and 85.7% respectively). The frequency of DKA was significantly higher in girls than in boys (59.3 vs. 40.7 %; $p < 0.05$), no such gender difference was encountered among members of the control group, indicating a higher risk of DKA among female (OR= 1.18). No significant differences were discovered between the two groups of patients regarding residency in urban or rural areas ($P>0.05$).

There was no association between DKA and family income; The mean monthly family income for cases of DKA was not significantly different ($P > 0.05$) from that of members of the control group (579,629 ± 406,736 and 616,071 ± 270,820 ID (ranging between 150,000 - 2,000,000 ID and 200,000 – 1,500,000 ID respectively); more than two thirds of patients with DKA (70.3%) had a monthly family income of 600000 ID and less as compared to 57.2% of the control group. At the same time DKA was not related to the parental educational level and family size; the mean parental educational level for cases and control was secondary school education for both parents and the mean number of households for cases and control group was 7.15 ±2.66 and 6.0 ± 2.33 respectively.

Family history of DM was discovered in 10 (37.0%) of cases, and 15 (53.6%) of the control group (Table 4).

Table 4: Family history of DM in the study groups.

Family member	Cases		Control	
	Frequency	Percentage	Frequency	Percentage
Father	1	3.7	4	14.3
Mother	-	-	1	3.6
Brother or sister	1	3.7	3	10.7
Other relative	8	29.6	7	25.0
None	17	63.0	13	46.4
Total	27	100	28	100

$P > 0.05$

Twelve (44.4%) of the episodes of DKA were in patients with known DM; in the other 15 (55.6%) of the cases, it was the first time they were discovered to be diabetic; newly discovered DM was encountered in 22 (78.6%) of the control group (Table 5).

Table 5: Diabetic history of the study groups.

Diabetic history	Cases		Control	
	Frequency	Percentage	Frequency	Percentage
Previously Diabetic	12	44.4	6	21.4
Newly diagnosed	15	55.6	22	78.6
Total	27	100	28	100

$P > 0.05$

Seven (58.3%) of the known diabetic patients in DKA group had history of previous attacks of DKA ranging from 1-7 attacks, All had had at least one episode of DKA in the previous two years of whom 5 (71.4%) within the last year; two patients (33.3%) of the diabetic patients in control group had a history of an attack of DKA (Table 6); Previous attacks of hypoglycemia were encountered in 10 (83.3%) of them, and 3 (50.0%) of the control group in patients those known to be diabetics (Table 7).

Table 6: Previous attacks of DKA among known diabetics within the study groups.

	Cases		Control	
	Frequency	Percentage	Frequency	Percentage
Yes	7	58.3	2	33.3
No	5	41.7	4	66.7
Total	12	100.0	6	100.0

$P > 0.05$

Table 7: Previous attacks of hypoglycemia among known diabetics within the study subjects.

	Cases		Control	
	Frequency	**Percentage**	**Frequency**	**Percentage**
Yes	10	83.3	3	50.0
No	2	16.7	3	50.0
Total	12	100.0	6	100.0

$P < 0.05$

Frequent urination with thirst for a day or more and fatigue, were the most common presenting symptoms for members of both cases of DKA and the diabetic patients of the control group accounting for more than 70% of patients in both groups with no statistical difference between them; while the occurrence of rapid breathing and/or shortness of breath, abdominal pain, fever, and nausea and vomiting were significantly higher among patients with DKA. The frequency of occurrence of the different symptoms among DKA cases and control group on admission is illustrated in table 8.

Table 8: Frequency distribution of different symptoms among the study subjects.

Symptom	**Cases**		**Control**	
	Frequency	**Percentage**	**Frequency**	**Percentage**
Frequent urination or thirst for a day	23	85.1	24	85.7
or more	19	70.4	20	71.4
Fatigue	17	63.0	2	7.1
Rapid breathing and/or shortness of	14	51.9	5	17.9
breath	13	48.1	3	10.7
Abdominal pain	11	40.7	6	21.4
Fever	8	29.6	10	35.7
Nausea and vomiting	6	22.2	-	-
Decreased appetite	3	11.1	1	3.6
Decreased consciousness	3	11.1	2	7.1
Fruity breath (breath odor)	2	7.4	-	-
Muscle stiffness or aching	2	7.4	5	17.9
Mental stupor that may progress to coma Headache				

The most common precipitating causes of DKA was infection, which occurred before,12 (44.4%) of the episodes, no identifiable cause for the episode was encountered in 7 (25.9%) of cases, missing the usual dose of insulin, and stress were identified in 3 (11.1%) for each, and increased food intake was documented as a precipitating factors in 2 (7.4%) of cases (Table 9).

Table 9: Possible precipitating factors of DKA.

Factor	Frequency	Percent
Infection	12	44.4
No identifiable cause	7	25.9
Missing doses of insulin	3	11.1
Stress	3	11.1
Increased food intake	2	7.4
Total	27	100

The mean temperature, and respiratory rate for patients with DKA were significantly higher than those of the control group ($P < 0.05$), while the mean heart rate was not significantly different between them (Tables 10).

Table 10: Frequency distribution of different signs among the study groups.

Sign	Cases		Control	
	Mean	SD	Mean	SD
Temperature* ……..°C	38.1	0.62	37.8	0.66
Heart rate: ……..…/min	98	9.85	95	8.12
Respiratory rate*: …….min	35	6.64	29	3.36

*$P < 0.05$

The weight status category seems to have no effect on the occurrence of DKA; the frequency distribution of the study subjects according to their weight status is shown in table 11.

Table 11: Distribution of the study subjects according to their weight status

Weight status category	Cases		Control	
	Frequency	Percentage	Frequency	Percentage
Under weight	7	25.9	12	42.9
Normal	17	63.0	13	46.4
Overweight	2	7.4	3	10.7
Obese	1	3.7	-	-
Total	27	100	28	100

$P>0.05$

Twenty six (96.3%) of the patients with DKA and two (7.2%) of the control group showed signs of dehydration; moderate to severe dehydration was encountered in 16 (59.3%) of the patients (Table 12).

Table 12: Signs of dehydration among cases of DKA.

Degree of dehydration	Cases		Control	
	Frequency	Percentage	Frequency	Percentage
None	1	3.7	26	92.8
Mild	10	37.0	1	3.6
Moderate	14	51.9	1	3.6
Severe	2	7.4	0	0
Total	27	100	28	100

The mean Blood glucose level was significantly higher *(P* < 0.05) in cases of DKA as compared to the control group, and the mean serum bicarbonate together with the mean blood PH was significantly lower *(P* < 0.05); the mean serum potassium was not significantly different between the two groups; the results of blood laboratory investigations of the studied subjects are shown in table 13.

Table 13: Blood chemistry and other laboratory investigations of the study groups.

Test	Cases		Control	
	Mean	SD	Mean	SD
Blood glucose (mg/dl)*	455	81.60	338	82.32
HCO3 (mmol/L)*	12.21	3.45	23.66	2.36
PH*	7.19	0.09	7.37	0.05
Serum potassium (m.Eq/l)	4.12	0.75	4.04	0.53

* *P* < 0.05

Patients with DKA showed a mean serum HCO3 level of 12.21± 3.45 m.Eq/L ranging from 5.6 – 17 m.Eq/L; they showed a mean serum PH level of 7.2 ± 0.089 m.Eq/L d ranging from 7.09 – 7.40 m.Eq/L .The frequency distribution of the different categories of DKA according to their serum HCO3 level are shown in tables 14 .

Table 14: Category of DKA according to HCO3 level.

DKA Category	Frequency	Percent
Mild	4	14.8
Moderate	15	55.6
Severe	8	29.6
Total	27	100

Mortality was null. Only 2 (8.3%) patients went into cerebral edema which improved on treatment (Table 15); all patients within the control group improved after the control of their state.

Table 15: prognosis of patients with DKA.

Prognosis	Frequency	Percent
Improved	25	92.6
Cerebral edema	2	7.4
Total	27	100

DISCUSSION

Similar to other studies, a clinical definition of diabetes type assigned by health care providers, the only one that could be applied to all of the patients, was used; the initial diagnosis was reported by pediatrician. All patients with DKA were classified as having T1DM; this can be explained by two facts, first T1DM is the main type of DM affecting adult and, second, it is the main type of DM associated with DKA in all age groups; in a study among Libyan diabetic patients with DKA 95% were classified as having T1DM.[43]

In contrast with previous studies.[44,45,46,47,48] the study found that the prevalence of DKA was not related to age in either gender, and it does not decrease with age; Rewers A et al (2002) from the University of Colorado, Denver, conducted a cohort study of 1,243 children with T1DM that showed an increased incidence of DKA with age in girls,[41] Some previous studies,[49] showed that children > 18 years face an increased risk of presenting in DKA, no similar result was concluded in this study; which can be explained by the small sample size of this study.

The increased risk of DKA among girls is consistent with the result of a the study conducted by Neu A et al (2003) in Germany,[49] no sex difference was recorded in other studies and, therefore, further larger studies are needed to elaborate the effect of gender on the prevalence of DKA among Iraqi

The result of this study is in contrast with previous studies that showed that adult in low-income families have higher rates of DKA,[45,47] There was no association between DKA and family income, therefore a field study among the general population is needed to elaborate the presence or absence of such association, for the accessibility of hospital consultation for those with low SES might have a confounding effect on such association.

The absence of an association between prevalence of DKA and parental educational level concluded in this study is dissimilar to that reported by Rewers A et al (2008) among youth from US population, which concluded an association with lower parental education,[45]

therefore, it can be concluded that the socio economic state has no effect on the prevalence of DKA in our population.; which is consistent with the other finding that there was no significant difference discovered between the two groups of patients regarding residency in urban or rural areas.

The finding that family history of DM was discovered in patients of the control group more than those with DKA indicates that it is not a predictor for DKA in diabetic children; no previous study could be found claiming that family history of DM is a predictor for DKA.
Newly discovered DM presenting for the first time as DKA involved a significant proportion (55.6%) of the cases of DKA studied, which is s higher than that concluded by Neu A et al (2003) in their study in Germany ,mentioned before, which was (26.3%),[49] and comparable to the results of Lakhdar et al (2005) among Libyan diabetic patients (78% of the episodes of DKA were in patients with known diabetes),[43] this might be explained by the better public awareness of symptoms of DM among Germans and, therefore, earlier diagnosis of DM before its possible complication of DKA.

The high frequency of previous attacks of complications of DM (i.e. DKA and hypoglycemia) encountered among DKA cases in this study might indicate the importance of the study of the different person variables of diabetic (including those of their families) in order to identify those at high risk, and thereafter, planning for prevention measures directed towards patients to avoid complications.

In this study, infection was the most common precipitating cause of DKA followed by increased food intake especially sweets; missing the usual dose of insulin and stressful conditions were documented as other less common factors together with first presentation with no identifiable cause for the episode. In Lakhdar A et al study (2005). The most common cause of DKA was stopping insulin therapy followed by first presentation and infection.[43] The high prevalence of infection can be explained on the basis of the high prevalence of infections in our country, as in other developing countries, and the health educational level among families of diabetic adult.

The weight status category was found to have no statistically significant effect on the occurrence of DKA; no previous study taking into account such factor into consideration could be found.

Taking either of the blood PH or the serum bicarbonate level into consideration, there was no effect of age on the severity of the episode of DKA; Roche E et al (2005) found that the very young (under 2 yr) are more likely to present in moderate to severe DKA.[50]

As some cases were admitted at night when blood gas analysis (BGA) was unavailable, clinical picture, high blood sugar and presence of ketonuria were used as the preliminary diagnostic criteria as the BGA were done in the next morning; this might explain the 3 patients with normal PH encountered in this study.

The high percentage of moderate- severe cases (more than 70% of cases) might be attributed to poor education of the family about the disease and its symptoms and the delay in consulting a doctor.

No death was recorded and the 2 (7.4%) patients with DKA who went into cerebral edema improved on treatment; in Lakhdar A et al study (2005) in Libya the mortality rate was 2%.[43] the small sample size might explain this difference.

CONCLUSIONS

The main predicting factors of the episodes of DKA concluded in this study are

Female gender, history of previous attack of DKA, especially within the last 2 years and history of previous attack of hypoglycemia.

The following factors were found to have no significant effect

Family income, parental education and weight status

The main precipitating factors for the episodes concluded in this study are in order

- Infection
- Increased food intake especially sweets
- Missing the usual dose of insulin
- Stressful conditions

Newly discovered DM presenting for the first time as DKA involved a significant proportion of the cases of DKA; this indicates the necessity of health education to improve public awareness of symptoms of DM for earlier diagnosis of DM before its possible complication

of DKA, and in the absence of community efforts to increase public awareness of the early symptoms of diabetes, DKA is likely to remain a major cause of morbidity.

It can be concluded that the majority of cases of DKA is potentially avoidable by simple education and is associated with a low mortality (if any) if good medical care is accessible.

RECOMMENDATIONS

Taking into consideration the concluded predicting and precipitating factors of DKA .Increased public awareness and greater medical alertness concerning the symptoms and signs of diabetes are warranted.

Also recommended that the education about how to care for a adult with diabetes must be provided to the entire family unit in order to protect him from the possible episode of DKA.

REFERENCES

1. James J. The diabetes health care team. In: Diabetes Care and Education Committee of the Banting and Best Diabetes Centre (BBDC). Approach to the management of diabetes mellitus. Banting and Best Diabetes Centre, Faculty of Medicine, University of Toronto, 2005.
2. Craig ME, Hattersley A, Donaghue K. ISPAD Clinical Practice Consensus Guidelines 2006–2007; Definition, epidemiology and classification, *Pediatric Diabetes*, 2006; 7: 343–351.
3. WHO. What are the risks of diabetes in children? Available at: www.who.int/features/qa/65/en/. Visited September 10, 2009.
4. Soltesz G, Patterson CC, Dahlquist G, EURODIAB Study Group. Worldwide childhood type 1 diabetes incidence – what can we learn from epidemiology? *Pediatric Diabetes*, 2007; 8(6): 6 – 14.
5. Alwan AA. Management of diabetes mellitus standards of care and clinical practice guidelines. WHO Regional Office for the Eastern Mediterranean 1994. Available at: www.emro.who.int/dsaf/dsa509.pdf.
6. Khatib OM. Guidelines for the prevention, management and care of diabetes mellitus. EMRO Technical Publications Series 32 Available at: www.emro.who.int/dsaf/dsa664.pdf, 2006.
7. Silverstein etal. Care of Children and Adolescents With Type 1 Diabetes A statement of the American Diabetes Association. *Diabetes Care J*, 2005; 28(1): 186 – 212.

8. Dunger DB, Sperling MA, Acerini CL, Bohn DJ, Daneman D, Danne TPA Savage O, Tasker RC, Wolfsdorf JI. ESPE/LWPES consensus statement on diabetic Ketoacidosis in children and adolescents. *Arch Dis Child*, 2004; 89: 188–194.
9. Dunger DB, Sperling MA, Acerini CL, Bohn, DJ, Daneman D,, Danne, TPA, Glaser NS, Hanas R, Hintz RL, Levitsky LLL, Savage MO, Tasker RC, Wolfsdorf JI. European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetic ketoacidosis in children and adolescents. *Pediatrics,* 2004; 113(2): 133-140.
10. Rajbhandari SM, Tesfaye S, Ward JD. Acute diabetic ketoacidosis precipitated by substitution of insulin in type 2 diabetes. *Practical Diabetes International*, 2005; 16(8): 253 – 254.
11. Balasubramanyam A, Zern JW, Hyman DJ, Pavlik V. New profiles of diabetic ketoacidosis: type 1 vs. type 2 diabetes and the effect of ethnicity. *Arch Intern Med,* 1999; 159(19): 2317 –2322.
12. Ko SH, Lee WY, Lee JH, Kwon HS, Lee JM, Kim SR, Moon SD, Song KH, Han JH, Ahn YB, Yoo SJ, Son HY. Clinical characteristics of diabetic ketoacidosis in Korea over the past two decades. *Diabetic Medicine,* 2008; 22(4): 466 – 469.
13. Zouvanis, Pieterse AC, Seftel HC, Joffe BI. Clinical Characteristics and Outcome of yperglycaemic Emergencies in Johannesburg Africans, *Diabetic Medicine,* 2004; 14(7): 603 – 606.
14. Chase HP, Garg SK, Jelley DH. Diabetic ketoacidosis in children and the role of outpatient management. *Pediatr. Rev.*, 1990; 11; 297-304.
15. Umpierrez GE, Kitabchi AE. Diabetic ketoacidosis: risk factors and management strategies. *Treat Endocrinol*, 2003; 2(2): 95-108.
16. Bui TP, Werther GA, Cameron FJ. Trends in diabetic ketoacidosis in childhood and adolescence: a 15-yr experience. *Pediatric Diabetes*, 2002; 3(2): 82 – 88.
17. Kitabchi A, Umpierrez G, Murphy M, Barrett E, Kreizberg R, Malone J, Wall B Management of hyperglycemic crises in patients with diabetes. *Diabetes Care*, 2001; 24(1): 131–153.
18. 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(5): 1150-1159.

19. Alemzadeh R and Wyatt DT. Diabetes mellitus in children in Kliegman RM, Behrman RE, Jenson HB, Bonita, Stanton ; Nelson Textbook of Pediatrics Saunders; 18 edition July 11, 2007: 2412-2414.
20. American diabetes association; cure, care, commitment. Ketoacidosis. Available at: http://www.diabetes.org/type-1-diabetes/ketoacidosis.jsp. Visited August 27, 2009.
21. Young GM. Pediatrics, Diabetic Ketoacidosis. *Medscap's Continually Updated Clinical Reference*. Available at: http://emedicine.medscape.com/article/801117-overview. Accessed August 27, 2009.
22. Linares MY, Schunk JE, Lindsay R. Laboratory presentation in diabetic ketoacidosis and duration of therapy. *Pediatr Emerg Care*, 1996; 12: 347 –351.
23. Monroe KW, King W, Atchison JA. Use of PRISM scores in triage of pediatric patients with diabetic ketoacidosis. *Am J Manag Care*, 1997; 3: 253 –258.
24. Luzi L, Barrett EJ, Groop LC, Ferrannini E, De Fronzo RA. Metabolic effects of low-dose insulin therapy on glucose metabolism in diabetic ketoacidosis. *Diabetes*, 1988; 37: 1470 –1477.
25. Adrogue HJ, Lederer ED, Suki WN, Eknoyan G. Determinants of plasma potassium levels in diabetic ketoacidosis. *Medicine*, 1986; 65: 163 –172.
26. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, RobackM, Malley R, Kuppermann, N. Risk Factors for Cerebral Edema in Children with Diabetic Ketoacidosis. *The New England Journal of Medicine*, 2001; 344: 264-269.
27. Okuda Y, Adrogue HJ, Field JB, Nohara H, Yamashita K. Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. *J Clin Endocrinol Metab*, 1996; 81: 314 –320.
28. Green SM, Rothrock SG, Ho JD, Gallant RD, Borger R, Thomas TL, Zimmerman GJ. Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. *Ann Emerg Med*, 1998; 31: 41 –48.
29. Roberts MD, Slover RH, Chase HP. Diabetic ketoacidosis with intracerebral complications. *Pediatr Diabetes*, 2001; 2: 109 –114.
30. Marcin JP, Glaser N, Barnett P, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. *J Pediatr*, 2002; 141: 793 –797.
31. Kamat P, Vats A, Gross M, Checchia PA. Use of hypertonic saline for the treatment of altered mental status associated with diabetic ketoacidosis. *Pediatr Crit Care Med*, 2003; 4: 239 –242.

32. Wolfsdorf J, Craig ME, Daneman D, Dunger D, Edge J, Lee WRW, Rosenbloom A, Sperling MA, Hanas R; ISPAD Clinical Practice Consensus Guidelines 2006–2007-Diabetic ketoacidosis; *Pediatric Diabetes*, 2007: 8(1): 28–42.
33. Agus MS, Wolfsdorf JI. Diabetic ketoacidosis in children. *Pediatr Clin North Am*, 2005; 52(4): 1147-63.
34. Kitabchi AE, Wall BM. Management of diabetic ketoacidosis. *American Family Physician*; August, 1999; 455-70.
35. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. Effectiveness of a prevention program for diabetic ketoacidosis in children: An 8-year study in schools and private practices. Diabetes Care, 1999; 22(1): 7-9.
36. Grey M, Boland EA, Davidson M, Li J, Tamborlane WV. Coping skills training for youth with diabetes mellitus has long-lasting effects on metabolic control and quality of life. *J Pediatr*, 2000; 137: 107 –113.
37. Rewers A, Chase HP, Mackenzie T, Walravens P, Roback M, Rewers M, Hamman RF, Klingensmith G. Predictors of acute complications in children with type 1 diabetes. *JAMA*, 2002; 287: 2511-2518.
38. Golden MP, Herrold AJ, Orr DP. An approach to prevention of recurrent diabetic ketoacidosis in the pediatric population. *J Pediatr*, 1985; 107: 195 –200. Levy-Marchal C, Patterson C, Green A; EURODIAB ACE Study Group. Europe and Diabetes. Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study. *European and Dibetes*. *Diabetologia*, 2001; 44(suppl 3): 875-80.
39. Brink SJ. Diabetic ketoacidosis. *Acta Pædiatrica*, 2008; 88(427): 14 – 24.
40. Bismuth E, Laffel L. Can we prevent diabetic ketoacidosis in children? *Pediatric Diabetes*, 2007; 8(6): 24 – 33.
41. Morris AD, Boyle DI, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. *Lancet*, 1997; 350: 1505 –1510.
42. Dave J, Chatterjee S, Davies M, Higgins K, Morjaria H, McNally P, Lawrence I, Blackledge H.Evaluation of admissions and management of diabetic ketoacidosis in a large teaching hospital. *Practical Diabetes International*, 2004; 21(4): 149 -153.
43. About BMI for children and teens. Available at http://www.cdc.gov/healthyweight/ assessing/bmi/childrens_bmi/about_childrens_bmi.html, visited 22 December, 2009.
44. Lakhdar A, Elhabroush S , Characteristics and outcome of ketoacidosis in Libyan diabetic patients , *Practical Diabetes International*, 2005; 16(6): 171 – 173.

45. Levy-Marchal C, Patterson C, Green A; EURODIAB ACE Study Group. Europe and Diabetes. Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study. *European and Dibetes*. *Diabetologia*, 2001; 44(suppl 3): 875-80.
46. Rewers A, Klingensmith G, Davis C, Petitti DB, Pihoker C, Rodriguez B, Schwartz ID, Imperatore G, Williams D, Dolan LM, Dabelea D. Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the search for diabetes in youth study. *Pediatrics,* 2008; 121: 1258-1266
47. Pinkey JH, Bingley PJ, Sawtell PA, Dunger DB, Gale EA. Presentation and progress of childhood diabetes mellitus: a prospective population-based study. The Bart's-Oxford Study Group. *Diabetologia*, 1994; 37(1): 70 –74[Medline].
48. Mallare JT, Cordice CC, Ryan BA, Carey DE, Kreitzer PM, Frank GR. Identifying risk factors for the development of diabetic ketoacidosis in new onset type 1 diabetes mellitus. *Clin Pediatr (Phila)*, 2003; 42(7): 591 –597.
49. Maniatis AK, Goehrig SH, Gao D, Rewers A, Walravens P, Klingensmith GJ. Increased incidence and severity of diabetic ketoacidosis among uninsured children with newly diagnosed type 1 diabetes mellitus. *Pediatr Diabetes,* 2005; 6(2): 79 –83.
50. Neu A, Willasch A. Ehehalt S. Hub R, Michael B. Ketoacidosis at onset of type 1 diabetes mellitus in children – frequency and clinical presentation. *Pediatric Diabetes,* 2003; 4(2): 77 – 81.
51. Roche EF, Menon A, Gill D, Hoey H. Clinical presentation of type 1 diabetes. *Pediatric Diabetes*, 2005; 6(2): 75 – 78.