INTRODUCTION

Type 1 diabetes mellitus (T1DM) has long been associated with the development of cardiovascular disease (CVD). Numerous epidemiological studies have observed that diabetic subjects had extremely high risks of developing atherosclerosis, acute coronary events, and stroke relative to the general population. This risk is attenuated with very good glycemic control; however, even very well-controlled patients retain considerably higher cardiovascular risk as compared to healthy matched controls ***(Tran et al., 2012).***

Diabetic ketoacidosis (DKA) is an important complication of childhood diabetes mellitus and the most frequent diabetes-related cause of death in children. It is defined as a serum glucose concentration greater than 300 mg/dl, the presence of ketones in the blood, a blood pH below 7.3, and a serum bicarbonate level below 15 mEq/L ***(Dunger et al., 2004).***

Diabetic ketoacidosis occurs in 25 to 40 percent of children with newly diagnosed type 1 diabetes mellitus and may later recur in association with illness or non-compliance with treatment ***(Glaser et al., 2001).***

Although heart disease in diabetes is characterized by extraordinary complex vascular, neuro-hormonal, and myocardial interactions, new paradigms begin to emerge. These paradigms include metabolic control of cardiac gene

expression, glucotoxicity and glucolipotoxicity ***(Taegtmeyer et al., 2002).***

Cardiovascular complications of diabetic ketoacidosis might play an important role in morbidity and mortality of affected children. Unfortunately, it may be passed unnoticed in lack of continuous cardiac monitoring ***(Orlowski et al., 2008).***

Although, profound acidosis may depress myocardial contractility and vascular smooth muscle tone, the occurrence of these effects to a clinically relevant degree has not been demonstrated in pediatric DKA. Moreover, hypotension in children who have DKA is rare ***(Glaser, 2005).***

In adults, severe diabetic ketoacidosis might be associated with myocardial necrosis even without any additional evidence of atherosclerosis leading to transient wall motion abnormalities and even ventricular arrhythmias. Possibility of such a significant clinical phenomenon was not studied yet in children ***(Møller et al., 2005).***

Although, clinically unrecognized myocardial injury had been reported in an unexpectedly high incidence in critically ill children (e.g. patients with pneumonia, sepsis, severe burn, venom intoxication and after trauma or major surgeries ***(Lipshultz et al., 2006).***

Nevertheless, little is known about myocardial injury in DKA, few studies reported some biomarker elevation during this acute metabolic decomponsation, unfortunately, without correlation of this elevation to concomitant electrocardiographic, hemodynamic and echocardiographic possible findings.

Aim of the Work

The aim of this study is to

1- Assess the hemodynamic status and cardiac functions in children with T1DM while having DKA.

2- Investigate the possibility of occurrence of myocardial injury in children suffering DKA.

3- Explore the difference between children with DKA at diagnosis and those with recurrent DKA as regard hemodynamic status, cardiac functions and possibility of myocardial injury.

4- Predict the possible risk factors for hypothesized myocardial injury.

5- Assess the reversibility of any found abnormalities after recovery.

DIABETIC KETOACIDOSIS (DKA)

Definition

DKA is defined as a serum glucose concentration greater than 300 mg/dL, the presence of ketones in the blood, a blood pH below 7.3 and a serum bicarbonate level below15mEq/L ***(Wolfsdorf et al., 2006).***

Classification

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) ***(Wolfsdorf et al., 2014).***

Frequency of DKA and precipitating factors

At disease onset

There is wide geographic variation in the frequency of DKA at onset of diabetes; rates inversely correlate with the regional incidence of type 1 diabetes mellitus (T1DM). Frequencies range from 15 to 70% in Europe and North America ***(Usher-Smith et al., 2012).***

DKA at diagnosis is more common in younger children and in children whose families that do not have ready access to medical care for social or economic reasons ***(Wolfsdorf et al., 2014)***.

Risk factors for DKA in newly diagnosed cases

They include younger age (<2years), delayed diagnosis, lower socioeconomic status, and countries with low prevalence of T1DM. Lower income and lower parental educational achievement were associated with higher risk of DKA. Lack of health insurance also is associated with higher rates (and greater severity) of DKA at diagnosis, presumably because uninsured subjects delay seeking timely medical care. Thus, younger and poorer children are disproportionately affected ***(Wolfsdorf et al., 2014).***

Recurrent DKA:

The risk of DKA in children and adolescents with established T1DM is 1–10 percent per person-years. Insulin omission, either inadvertently or deliberately, is the commonest cause. There is usually an important psychosocial reason for omitting insulin ***(Wolfsdorf et al., 2014).***

Risk factors for DKA in established cases

The risk is increased in children with poor metabolic control or previous episodes of DKA, peripubertal and adolescent girls, children with clinical depression or other psychiatric disorders (e.g. eating disorders), children with difficult or unstable family circumstances (e.g., parental abuse) and children with limited access to medical services. An intercurrent infection is seldom the cause when the

patient/family is properly educated in diabetes management and is receiving appropriate follow-up care by a diabetes team with a 24 hours telephone help line ***(Wolfsdorf et al., 2014).***

In Egypt, however, the commonest risk factors for DKA were delayed diagnosis for newly diagnosed cases, moreover, insulin omission and infections in established one ***(Ahmed, 2012).***

Epidemiology

The worldwide variation in the incidence of DKA at presentation of T1DM in children has been well characterized by the WHO's Diabetes Mondialev (DiaMond) project, using standardized incidence data from 57countries from 1990 onwards which is illustrated in figure (1) ***(Usher-Smith et al., 2012)***

Although the frequency of DKA as a first manifestation of T1DM is higher in developing compared to developed countries, there is paucity of information on its characteristics in developing countries ***(Onyiriuka and Ifebi, 2013).***

In a descriptive study conducted on 416 patients of T1DM at Children's hospital, Ain Shams University; 60.5% of cases were presented by diabetic ketoacidosis ***(Ismail et al., 2008).***

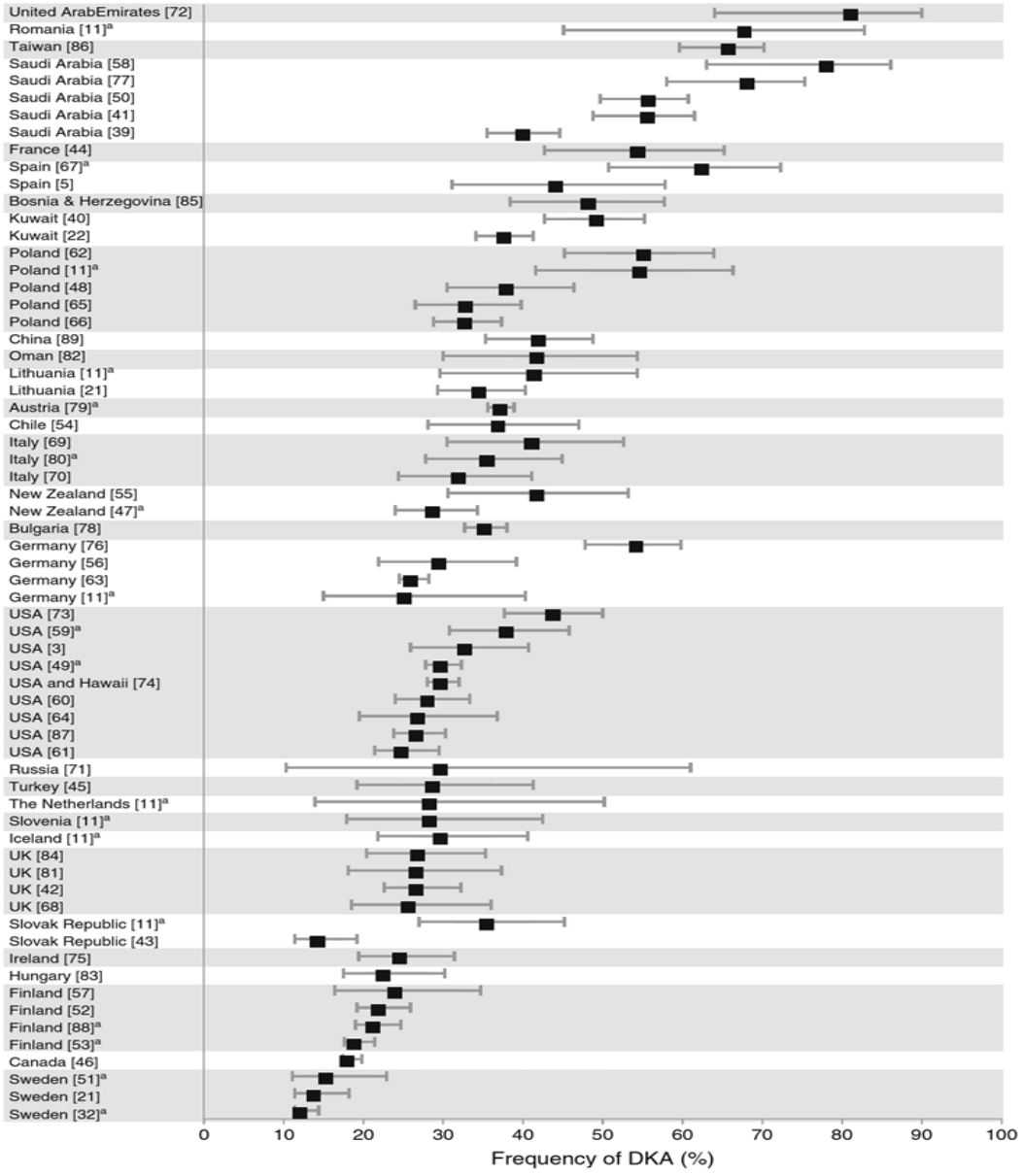

Fig. (1): Plot of the frequency of DKA at time of T1DM diagnosis in 57 countries ***(Quoted from Usher-Smith et al., 2012).***

Mortality

The mortality rate in children presenting with DKA is approximately 0.15–0.30%; the majority (60–90%), occurs in the setting of cerebral edema ***(Wolfsdorf et al., 2014).***

Pathophysiology

The adage "A child is not a miniature adult" is most appropriate when considering the pathophysiology of DKA. The child differs from the adult in a number of pathophysiological characteristics:

1) The younger the child, the more difficult it is to obtain the classical history of polyuria, polydipsia, and weight loss. Infants and toddlers in DKA may be misdiagnosed as having pneumonia, reactive airways disease (bronchial asthma), or bronchiolitis and therefore treated with glucocorticoids and/or sympathomimetic agents that only compound and exacerbate the metabolic derangements. Because the diagnosis of diabetes is not suspected as it evolves, the duration of symptoms may be longer, leading to more severe dehydration and acidosis and ultimately to obtundation and coma.

2) The higher basal metabolic rate and large surface area relative to total body mass in children requires greater precision in delivering fluids and electrolytes. The degree of dehydration is expressed as a fraction of body weight, i.e., 10% dehydration implies 10% loss of total body weight as water.

3) Cerebral and other auto regulatory mechanisms may not be as well developed in younger children. Hence, greater

severity at presentation in younger children together with less maturity of auto regulatory systems combine to predispose children to more serious complications.

4) Whereas delay in diagnosis is the major cause of DKA in previously unrecognized disease in younger children, omission of insulin is the leading cause of recurrent DKA, most prevalent among adolescents especially in girls ***(Jeha and Haymond, 2014)***.

The pathophysiological process in DKA is illustrated in figure (2)

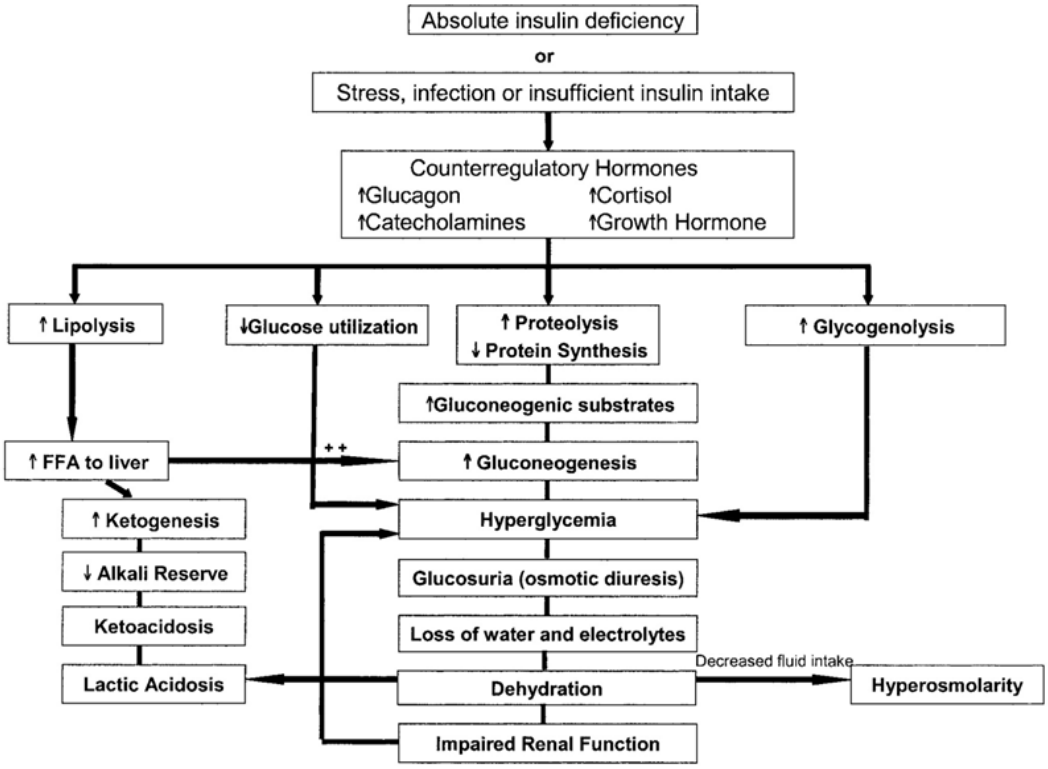

Fig. (2): Pathophysiology of DKA
(Quoted from Wolfsdorf et al., 2006)

Recently, in patients with DKA increased concentration of D-lactate and also of L-lactate had been reported. The concentration of D-lactate was similar to the concentration of beta-hydroxybutyrate. This was a surprise for many diabetologists as there are increased amounts of 36 organic acids in the blood and urine of patients with DKA. There are no reports on the dependency of these 34 previously "unidentified acids" on insulin and also no reports on the influence of insulin therapy on these acids. The mutual relation of these 36 acids is variable, including severe acidosis without acetoacetic and beta-hydroxybutyric acids. Thus, life-threatening acidosis and coma can develop also without increased concentration of these two acids, usually considered as insulin-dependent. The role of insulin in the pathophysiology of coma in DKA has been doubtful already earlier after reports on "euglycemic ketoacidosis" and even DKA with hypoglycemia. It is difficult to assume insulin deficiency in patients with "euglycemia" and "hypoglycemia". On the other hand, one can assume absolute deficiency of insulin after pancreatectomy: surprisingly, there is absence of the lethal ketoacidotic coma ***(Rosival, 2014).***

Diagnostic evaluation

The clinical diagnosis of diabetes in a previously healthy child requires a high index of suspicion. Signs and symptoms of DKA are related to the degree of hyperosmolality, volume depletion, and acidosis also history of DM for recurrent cases ***(Jeha and Haymond, 2014)***.

A) *Signs and symptoms*

The earliest symptoms of DKA are related to hyperglycemia. Older children and adolescents typically present with polyuria (due to the glucose-induced osmotic diuresis), polydipsia (due to the increased urinary losses), tachycardia, and fatigue. Other findings include weight loss, nocturia (with or without secondary enuresis), daytime enuresis, and vaginal or cutaneous moniliasis. Hypovolemia may be severe if the urinary losses are not replaced ***(Jeha and Haymond, 2014)***.

In infants, the diagnosis is more difficult because the patients are not toilet trained and they cannot express thirst. As a result, polyuria may not be detected and polydipsia is not apparent. However, decreased energy and activity, irritability, weight loss, and physical signs of dehydration are common findings. In addition, severe Candida diaper rash or otherwise unexplained metabolic acidosis or hypovolemia should heighten the suspicion for diabetes ***(Jeha and Haymond, 2014)***.

A number of other clinical findings may be seen e.g. Polyphagia with anorexia, nausea, vomiting, and abdominal pain, deep (Kussmaul) respirations tachypnea and a fruity breath smell. Neurologic findings, ranging from drowsiness, lethargy, and obtundation to coma, are related to the severity of hyperosmolality and/or to the degree of acidosis ***(Jeha and Haymond, 2014)***.

B) Laboratory testing:

- **Serum glucose**: The serum glucose is, by definition, greater than 200 mg/dL.
- **Acid-base status:** The second criterion for the diagnosis of DKA is a serum bicarbonate <15 mEq/L or a venous pH <7.3. Acetoacetic acid is the initial ketone formed and it may be reduced to beta-hydroxybutyric acid (another organic acid) or decarboxylated to acetone, which will be detected as a ketone but does not contribute to the acidosis.
- **Conventional ketone urine screening tests:** These tests are performed with nitroprusside impregnated strips or tablets (Acetest). Nitroprusside reacts with acetoacetate and acetone but not beta-hydroxybutyrate. In DKA, beta-hydroxybutyrate makes up 75 percent of the circulating ketones. Thus, clinical testing with nitroprusside may underestimate the severity of ketoacidosis and ketonuria. On the other hand, during recovery beta-hydroxybutyrate is converted to acetoacetate and acetone, which persist for a longer period. As a result, urine testing may give a false impression of persistent ketoacidosis. Therefore, direct measurement of beta-hydroxybutyrate should be used whenever possible.
- **Blood testing for beta-hydroxybutyrate:** As a point of care, ketone-meter measures a current produced during oxidation of beta-hydroxybutyrate to acetoacetate, and is accurate in children and adults in a variety of clinical settings for plasma beta-hydroxybutyrate concentrations of up to 52 mg/dl.

- **The Anion Gap (AG)** It is useful in estimating the severity of ketosis, and its normalization is a direct measure of the resolution of ketoacidemia. The serum anion gap is calculated from the following formula in units of mEq/L or mmol/L: Serum anion gap = Serum sodium - (Serum chloride + bicarbonate).The normal value in children is 12±2 mmol/L
- **Blood urea nitrogen:** Patients with severe hypovolemia often have elevated blood urea nitrogen concentrations. This finding at presentation may have predictive value since it is a risk factor for cerebral edema during therapy
- **Serum sodium:** The serum sodium concentration is affected by hyperglycemia. The magnitude of this effect is determined by two major factors.
    - Hyperglycemia will increase the plasma osmolality, resulting in osmotic water movement out of the cells which lowers the serum sodium by dilution. Theoretical calculations suggest that the serum sodium should be lowered by 1.6 mEq/L for every 100 mg/dL elevation in serum glucose.
    - The direct effect of hyperglycemia to lower the serum sodium is counteracted to a variable degree by the glucosuria-induced osmotic diuresis. The diuresis results in water loss in excess of sodium and potassium, which will tend to raise the serum sodium concentration and plasma osmolality. Inadequate water intake, which may

be a particular problem in hot weather and in infants and young children who cannot independently access water, prevents partial correction of the hyperosmolality and can even lead to hypernatremia despite the presence of hyperglycemia. On the other hand, consumption of large volumes of dilute fluid, since thirst is stimulated by hyperosmolality, can contribute to hyponatremia. A third factor that can affect the measured serum sodium concentration represents a laboratory artifact. Hyperlipidemia can cause pseudohyponatremia by reducing the fraction of plasma that is water.

- **Serum potassium**: The osmotic diuresis and increased ketoacids excretion promote urinary potassium loss, while vomiting and diarrhea, if present, increase gastrointestinal potassium losses. Potassium loss in children appears to be 6 to 7 mEq/kg. The potassium losses will tend to produce hypokalemia. However, the combination of insulin deficiency, which impairs potassium entry into the cells, and hyperosmolality, which pulls water and potassium out of the cells, tends to raise the serum potassium concentration. Ketoacidosis itself proved to have little effect on transcellular potassium movement on contrast to the previously adopted. As a result, serum potassium at the time of presentation can be normal, increased, or decreased ***(Jeha and Haymond, 2014)***.
- **Serum phosphate:** Children with DKA are typically in negative phosphate balance as demonstrated in figure (3) because of decreased phosphate intake and phosphaturia