Prognosis of chronic complications of diabetes mellitus (DM) after multiple events of diabetic ketoacidosis (DKA)

Baraa Faiez Rajab1*, Anwar Essa Alamrim1, Ali Essa Alamri2

ABSTRACT

The uncontrolled type 1 or type 2 diabetic patients may develop diabetic ketoacidosis (DKA). DKA is associated with a wide range of complications, including the brain, lung, coagulation pathway, and gastrointestinal tract. This review is concerned with a chronic complication of diabetes mellitus (DM) after multiple events of DKA.

Keywords: Diabetes mellitus (DM), diabetic ketoacidosis (DKA), complications, cerebral edema, pulmonary edema.

Introduction

Diabetes is recognized as a major health burden in Saudi Arabia. More than 3.4 million citizens were diagnosed with diabetes in the year 2015 [1,2]. Numerous variables have been included in the etiology of the disease and most of them are directly related to disorders of insulin production, its action or both. The resulting failure of glucose uptake by human cells leading to hyperglycemia can start a series of severe metabolic changes and chronic organ dysfunctions. Different categories of diabetes were identified: type (1), type (2), gestational diabetes, and diabetes resulting from other conditions such as pancreatitis or consumptions of large doses of exogenous steroids [2]. Diabetic ketoacidosis (DKA) is a metabolic imbalance which is characterized by the presence of ketosis, hyperglycemia, metabolic acidosis, and hyperketonemia and it occurs mainly in T1D patients; however, type 2 diabetes patients with metabolic decompensation could develop DKA [3], it is considered to be one of the most severe complications of diabetes mellitus, especially type 1 diabetes mellitus (DM) [4]. The yearly prevalence of DKA is reported to range from four to eight episodes per 1,000 patient diagnosed with diabetes [5]. The prevalence of DKA in the US continues to increase and it is accounted that about 140,000 hospitalizations are reported in 2009 which had yet again increased to 168,000 to hospitalizations [6,7]. The 2014 DKA hospitalization rates were the highest in individuals aged <45 years (44.3/1,000) and lowest in individuals aged ≥65 years (<2.0/1,000) [8]. The rate of hospital admissions for the hyperglycemic hyperosmolar syndrome (HHS) is lower than that of DKA and is less than 1% for all diabetic-related admissions [9,10].

Diabetic ketoacidosis is diagnosed in different ways but the typical method of diagnosis includes the following three factors: elevated plasma glucose (>250 mg/dl), ketones in serum or urine, and acidosis (serum bicarbonate < 18 mEq/L and/or pH < 7.30) [11]. Management of DKA includes fluid and electrolyte therapy, insulin therapy, treatment of any identified triggering causes (e.g., continuous subcutaneous insulin infusion pump failure, sepsis, pneumonia, acute pancreatitis, cerebrovascular accident, myocardial infarction, stroke, trauma, medications that affect carbohydrate metabolism), and monitoring of therapy and resultant complications [11]. Complications of DKA management include pulmonary venous congestion and severe electrolyte imbalance. Cerebral edema represents a major potential complication although this has largely been demonstrated in children [12]. This article is aimed at reviewing the literature available on the prognosis of chronic complications of DM after multiple events of DKA.

Data Collection

A web-based literature search using the advanced features of various databases such as PubMed, Scopus, Embase,
Google Scholar, Directory of Open Access Journals, and Cochrane electronic databases was carried out. The major MeSH and other keywords like “Prognosis of a chronic complication of diabetes mellitus,” “the correlation between DM and DKA,” “prevalence of DKA,” “complications of frequent DKA” were used. The search included articles published between 1980 and 2018, and the search was limited to articles published in the English language.

**Pathophysiology Diabetic Ketoacidosis**

DKA is a complex metabolic disease characterized by hyperglycemia, acidosis, and ketonemia. DKA usually occurs as a result of absolute or relative insulin deficiency that is accompanied by an increase in counterregulatory hormones (i.e., glucagon, cortisol, growth hormone, and catecholamines). This type of hormonal imbalance improves hepatic gluconeogenesis and glycogenolysis resulting in severe hyperglycemia. Enhanced lipolysis increases serum free fatty acids that are then metabolized as an alternative energy source in the process of ketogenesis [13]. These outcomes result in the formation of large amounts of ketone bodies and ensuing metabolic acidosis. Ketones incorporate acetone (CH3)CO, 3-beta-hydroxybutyrate, and acetoacetate. The dominating ketone in DKA is 3-beta-hydroxybutyrate. DKA has been viewed as demonstrative, or even symptomatic of type 1 diabetes, however, progressively there are cases of ketone-prone type 2 diabetes being identified. But, the essential treatment is the same. There are different mechanisms responsible for fluid depletion in DKA. These incorporate osmotic diuresis because of hyperglycemia, vomiting commonly connected with DKA, and in the end, it could result in failure to take in the fluid because of a decreased level of awareness. Electrolyte shifts and consumption are in part related to the osmotic diuresis. Hyperkalemia and hypokalemia require specific consideration [13].

**Mortality and Morbidity**

An enhanced comprehension of the pathophysiology of DKA together with close monitoring and rectification of electrolytes has to lead to a significant decrease in the general death rate from this hazardous condition. Mortality rates have fallen fundamentally over the recent 20 years from 7.96% to 0.67% [14]. The mortality rate is still high in developed countries and among non-hospitalized patients [15]. This high mortality rate shows the necessity of early analysis and the execution of effective prevention programs. Cerebral edema remains the most well-known reason for mortality, especially in young children and adolescents. The primary cause of mortality in the adult populace incorporates severe hypokalemia, adult respiratory distress disorder, and co-morbid states, for example, pneumonia, acute myocardial infarction, and sepsis [16].

**Chronic Complications of DKA and their Treatment**

**Cerebral edema**

Cerebral edema as a complication of diabetic ketoacidosis (CE-DKA) was first described by Dillon et al. [17]. Although initially reported in adults [18], it was considered to be much more common in children and accounts for the majority of the morbidity and mortality associated with DKA in this age group [19]. The reported occurrence rate in the pediatric literature varies between 0.2% and 1% [20]. However, this is likely to be an underestimate as it is based on retrospective reviews relying on the clinical observation of increased intracranial pressure. The incidence also is reported to be higher in new-onset diabetes and in younger children [21]. Series of brain imaging studies in children with DKA have shown decreased ventricular size either early (<12 hours) in the treatment course [22] or even before therapy has commenced [23]. The sequelae of this, namely brain stem herniation, have been reported to be 5.8% (9/153) in one series of all children presenting with DKA [24]. The total adverse outcome rate (death or permanent neurological injury) in CE-DKA is as high as 40%–50% in some series with few intact survivors where brain stem herniation has occurred [25]. Many theories have been advanced to explain brain swelling in association with DKA, including overzealous rehydration with hypotonic intravenous fluids, the rapid reduction of blood glucose with insulin, activation of the Na/H transporter system, change in oncotic pressure, increased permeability of the blood–brain barrier, and changes in cerebral blood flow [26].

**Respiratory system complications of KDA**

**Hydrostatic pulmonary edema in DKA**

Hydrostatic pulmonary edema is normally determined during the presentation of DKA or severe hyperglycemia without DKA and is usually cured during the management of these disorders. The sequence of aspiratory edema at introduction with severe hyperglycemia with or without DKA and its rectification with insulin organization have been accounted for patients with advanced renal failure [27]. Improvement of circulatory overload and hydrostatic aspiratory edema in these patients was initially ascribed to the acute shift of a significant volume of fluid from the intracellular into the extracellular compartment. This volume shift is an osmotic result of solute accumulation in the extracellular compartment during advancement of hyperglycemia. A remedy of hyperglycemia with insulin organization is shifting fluid back into cells [28].

**Non-hydrostatic pulmonary edema in DKA**

Diabetes mellitus may influence the structure and function of the lungs and other major organs. Histological changes in the lungs of diabetic patients include the alveoli and the pneumatic branched vessels, while the most consistent
practical changes that would occur are diminished lung volumes, decreased pulmonary elastic recoil, and decreased capillary lung volume prompting debilitated diffusion capacity [29]. Respiratory capacity in these patients is usually preserved under ordinary conditions but their lung saves are diminished and can cause clinical lung dysfunction under unpleasant conditions, including volume overload [30].

**DKA and Arrhythmias**

Fluid and electrolyte imbalance is the most abundant condition occurring in DKA and commonly shows as loss of 5–8 l of water, 400–700 mEq of sodium, 250–700 mEq of potassium, and 30–50 mEq of magnesium. But, the overall loss of water is in an overabundance of the electrolytes, and thus most patients will have normal or even increased levels of sodium, potassium, and magnesium at the time of presentation, even though the body stores of these elements are always below the normal [31]. Potassium deficiency is one of the most important of electrolyte disturbance found in DKA because it can cause fatal arrhythmias. Basic levels of potassium may be normal or increased, but after 12 hours of treatment, most patients would become hypokalemic in the absence of replacement potassium; serial electrocardiogram (ECG)’s may be useful in the early investigation of hypokalemia or hyperkalemia. Hypokalemia is related to ECG impairments and cardiac arrhythmias, especially when the serum potassium level is less than 3 mEq/L. The most abundant and may be the earliest ECG finding in hypokalemia is a prominent U wave, typically clear in leads II and III atrioventricular fistula (AVF). Stress factors (ST) depression and T inversion can likewise happen, similar to myocardial ischemia. The most widely recognized heart arrhythmias are atrial premature contractions, atrial tachycardia with or without atrioventricular (AV) block, supraventricular tachycardia, and ventricular premature contractions. Less abundant are AV junctional tachycardia or escape rhythm and AV block [32].

**DKA and Coagulopathy Complications**

DKA mainly involves glucose metabolism; where it has a direct link with the systemic inflammatory response portrayed by vascular endothelial damage and coagulopathy. The inflammatory state associated with DKA is characterized by increased levels of inflammatory markers C-reactive protein, cytokines [Illinois diabetes-6 (IL6), IL1β], and tumor necrosis factor-α (TNFα), and their complement activation [33]. Almost certainly, the oxidative stress prompted by hyperglycemia and ketosis [34] adds to this inflammatory response and results in diffusion of vascular damage. Proof of vascular endothelial damage can be found in pre-treatment subclinical cerebral edema (CE) [35], pulmonary interstitial edema [36], disseminated intravascular coagulation [37,38], and increased levels of thrombomodulin [38]. The vascular endothelium is an essential target for the impaired glycemic metabolism in T1DM [39]. Kids with T1DM might be in danger of a chronic condition of inflammation and endothelial activation outside of the episode of DKA. Kids within 1 year of diagnosis have been investigated to have biochemical proof of inflammation, with elevated levels of both serum prothrombin concentration and TNFα compared with kids above 1 year of post-diagnosis and to nondiabetic controls [40]. Moreover, this report provides definite proof for endothelial disturbance, described by levels of Von Willebrand Factor and tissue plasminogen activator more than two standard deviations higher than control. Another investigation found that the endothelial cell-specific adhesion particle and soluble endothelial leukocyte adhesion molecule (SE-Selectin) were observed to be increased in kids with type 1 diabetes compared with healthy controls and was directly related to serum glucose levels [41]. Investigation of the coagulation system in adult diabetic patients has also recognized abnormalities in the coagulation system [42].

**Gastrointestinal Complications of DKA**

Gastrointestinal symptoms, like nausea, vomiting, abdominal pain, and distension, are reported in about 50%–75% of patients who are diagnosed with DKA [43,44]. Not exceptionally, these symptoms control the clinical picture at the time of DKA development, leading, in some cases, to a delay in treatment with fluids and insulin. On uncommon events, uncomplicated DKA might be associated with physical signs suggestive of an acute surgical abdomen [44]. In some cases, unnecessary, dangerous surgical intervention has been performed, especially among the previously undiagnosed diabetic patients [45]. As most cases of the gastrointestinal manifestations of DKA are resolved instantly with suitable therapy of the metabolic abnormalities, it is incumbent on the physician to differentiate gastrointestinal symptoms resulting from DKA from those caused by an active intra-abdominal process (e.g., cholecystitis, peritonitis, vascular compromise, or pancreatitis). In such manner, it is a must to make sure that fatalities from DKA frequently come from underlying non-diabetic medical and/or surgical emergencies which may go unrecognized because of the seriousness of the metabolic impairments or its depressive consequences for mental function [46].

Acute neuropathy after ketoacidosis is a rare complication and its pathogenesis is not clear. Patients with diabetic ketoacidosis require careful monitoring of neurological function, even after normalization of their glycemic parameters [47]. Diabetic neuropathy is deemed to be secondary to the deposition of metabolic products of hyperglycemia, in neurilemmal sheaths [48]. Hyperglycemia is the only modifiable risk factor for diabetic neuropathy. Glycemic control reduces the incidence of neuropathy, slows its progression, and improves the quality of life for diabetic patient’s [49,50].
Other studies have shown associations of neuropathy with age, duration of disease, and metabolic control. Few of them have also looked into the association of neuropathy with male gender, age, and glycemic control [47].

**Conclusion**

The most widely recognized complication of DKA is cerebral edema and its pathogenesis is still under study. Other less dominant complications include pulmonary edema, arrhythmias, coagulopathy, and gastrointestinal problems. The early diagnosis and treatment of these diseases are helpful in preventing its chronicity. More data related to the presentation, treatment, and outcomes of these complications in DKA patients are still required. Therefore, avoidance of DKA in children and adolescents through public and professional awareness is paramount in preventing these chronic complications.

**List of Abbreviations**

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<tr>
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<tr>
<td>AV</td>
<td>Atrioventricular</td>
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<td>CE-DKA</td>
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<td>CE</td>
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<td>DKA</td>
<td>Diabetic ketoacidosis</td>
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<td>DM</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>HHS</td>
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**Conflict of interest**

The authors declare that there is no conflict of interest regarding the publication of this article.

**Funding**

None.

**Consent for publication**

Not applicable.

**Ethical approval**

Not applicable.

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**References**

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