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The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management

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ARTICLE INFO

Article history:
Received 6 October 2015
Accepted 16 December 2015

Keywords:
Diabetic ketoacidosis
Etiology
Pathogenesis
Management

ABSTRACT

The prognosis of diabetic ketoacidosis has undergone incredibly remarkable evolution since the discovery of insulin nearly a century ago. The incidence and economic burden of diabetic ketoacidosis have continued to rise but its mortality has decreased to less than 1% in good centers. Improved outcome is attributable to a better understanding of the pathophysiology of the disease and widespread application of treatment guidelines. In this review, we present the changes that have occurred over the years, highlighting the evidence behind the recommendations that have improved outcome. We begin with a discussion of the precipitants and pathogenesis of DKA as a prelude to understanding the rationale for the recommendations. A brief review of ketosis-prone type 2 diabetes, an update relating to the diagnosis of DKA and a future perspective are also provided.

1. Background

Diabetic Ketoacidosis (DKA) is a potentially fatal metabolic complication of uncontrolled diabetes mellitus. In his first clinical description of diabetes mellitus in the 2nd Century A.D. Aretaeus gave a detailed account of subjects with hyperglycemic crises [1], but it was Julius Dreschfeld, a German pathologist who further characterized DKA in his lecture to the Royal College of Physicians in London in 1886. He reported on the main ketones, acetoacetate and β-hydroxybutyrate, and their chemical determination [2]. The incidence of DKA in developed countries is comparable with estimated annual incidence rate of 13.6 and 14.9 per 1000 type 1 diabetic patients in the UK [3] and Sweden [4] respectively and 13.4 per 1000 subjects younger than 30 years in the US [5]. Hospital admission for DKA has increased by about 75% over the last two decades in the USA from about 80,000 in 1988 to 140,000 in 2009 [6].

DKA was invariably fatal until the discovery of insulin in the 1920s; however, DKA related mortality has reduced significantly over the years. In the US, the age-adjusted mortality rate decreased 64% from 48.4 per 100,000 diabetic population in 1980 to 17.3 per 100,000 diabetic population in 2009 [6]. Mortality was also reported to be low in the Europe with one UK institution recording no deaths amongst 46 DKA patients between 1997 and 1999 [3]. Overall, the mortality in adults in the UK and USA is less than 1% [3,6], but may be higher than 5% in the elderly and patients with severe co-morbid conditions [7,8]. DKA remains a leading cause of mortality in children and young adults with type 1 diabetes [9,10]. Morbidity and mortality from DKA remain high in developing countries, with incidence of about 80 per 1000 diabetic admissions and mortality rate of 30% in Kenya [11] and incidence of 41.7 per 100,000 population and mortality rate of 11.7% in Libya [12]. DKA is economically burdensome with an average length of stay of 3.4 days, DKA is responsible

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http://dx.doi.org/10.1016/j.metabol.2015.12.007
0026-0495/

Table 1 – Diagnostic criteria and typical total body deficits of water and electrolytes in diabetic ketoacidosis.

	Mild	Moderate	Severe
Diagnostic criteria and classification			
Plasma glucose (mg/dl) [+]	>250	>250	>250
Arterial pH	7.25–7.30	7.00- < 7.24	<7.00
Serum bicarbonate (mEq/L)	15–18	10- <15	<10
Urine ketone [*]	Positive	Positive	Positive
Serum ketone [*]	Positive	Positive	Positive
Effective Serum Osmolality [**]	Variable	Variable	Variable
Anion Gap [***]	>10	>12	>12
Mental Status	Alert	Alert/Drowsy	Stupor/Coma
Typical deficits			
Total Water (L)	6		
Water (ml/kg) [δ]	100		
Na + (mEq/kg)	7–10		
Cl- (mEq/kg)	3–5		
K+ (mEq/kg)	3–5		
PO4 (mmol/kg)	5–7		
Mg++ (mEq/kg)	1–2		
Ca++ (mEq/kg)	1–2		

[+] Euglycemic DKA has been reported.
[*] Nitroprusside reaction method.
[**] Calculation: Effective serum osmolality: 2[measured Na + (mEq/L) + glucose (mg/dl)/18 [mOsm/kg].
[***] Calculation: Anion Gap: $(Na^+)-(Cl^- + HCO_3^-$ (mEq/L) [normal =12 ± 2].
[δ] Per kg of body weight. Data adapted from ref [19].

for about half a million hospital days per year and an estimated annual direct and indirect cost of 2.4 billion USD [6,13].

DKA consists of the biochemical triad of hyperglycemia, ketonemia and metabolic acidosis (table 1) resulting from absolute or relative insulin deficiency in the presence of an increase in counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). Although DKA is typically characterized by hyperglycemia, euglycemic DKA has been reported in patients with type 1 diabetes who were vomiting, fasting or had been treated with insulin prior to presentation, and in pregnancy [14,15]. Additionally, there has been recent reports of euglycemic DKA in subjects treated with sodium–glucose cotransporter 2 (SGLT2) inhibitors [16,17].

DKA is more common in subjects with type 1 diabetes; but can also occur in type 2 diabetes, especially in patients of African or Hispanic descent [18]. About 35% of DKA cases in the USA in 2006 occurred in people with type 2 diabetes [6]. Similarly, a study from Sweden noted that type 2 diabetes accounted for 32% of 26 episodes of DKA recorded in that Caucasian population, furthermore, in 50% of patients with type 2 diabetes, DKA was the initial manifestation of diabetes [4].

2. Precipitating Factors

A diligent investigation for the precipitating illness should be made in all cases of DKA, as effective treatment of these conditions contributes to better outcome. Mortality in DKA is usually related to the associated co-morbidity rather than the biochemical derangement. Omission or inadequate dosing of insulin and infection are the most common precipitants of DKA [19]. More recent reports may suggest that omission of insulin, which is preventable, is becoming a more frequent precipitant of DKA than infections. Intercurrent illness such as cerebrovascular accident, pancreatitis, myocardial infarction, trauma, and drugs are well known to trigger DKA. Drugs that affect carbohydrate metabolism such as corticosteroids, thiazides, and sympathomimetic agents like dobutamine and terbutaline as well as atypical antipsychotic agents could precipitate DKA in susceptible individuals [20]. Subjects with type 1 diabetes using amphetamine-like analogs may be predisposed to DKA due to elevated catecholamine levels [21]. Emerging data suggests Sodium-Glucose Cotransporter 2 Inhibition may increase the risk of DKA, prompting the FDA to issue a warning in this regard in May 2015 [16,22]. Twenty cases of DKA were reported with SGLT-2 inhibitors in patients with diabetes in the FDA Adverse Event Reporting System (FAERS) between March 2013 and June 6, 2014. The mechanism of DKA in subjects treated with SGLT2 is not known with certainty; putative mechanisms include reduced insulin dose, glucagon secretion and decreased excretion of ketone bodies [22]. In young patients with type I diabetes, psychological problems complicated by eating disorders may be a contributing factor in 20% of recurrent ketoacidosis. Other factors that may lead to insulin omission and DKA in younger patients include fear of weight gain and hypoglycemia, rebellion against authority and the stress of chronic disease [23]. Cocaine use was reported as an independent risk factor for recurrent DKA in a retrospective study of over 200 cases of DKA [24]. Another study of a large cohort of DKA patients observed that substance abuse especially cocaine but also alcohol and cannabis were associated with recurrent episodes of DKA [25]. A recent report [26], suggested a relationship between low carbohydrate dietary intake and metabolic acidosis. Additionally, mechanical problems with continuous subcutaneous insulin infusion devices (CSII) has also been associated with DKA [27]. Finally, DKA has also been reported as the initial manifestation of previously undiagnosed endocrine conditions like acromegaly [28] and pheochromocytoma [29,30].

3. Ketosis-Prone Type 2 Diabetes

African authors reported about temporary diabetes in adults in the 1960s, subjects who after an episode of DKA could maintain glycemic control for varying periods without insulin therapy [31,32]. More recently, an increasing number of DKA cases with no apparent precipitating factors have been reported in subjects with type 2 diabetes; studies have indicated that about half of previously undiagnosed adult African Americans (AAs) and Hispanic subjects with unprovoked DKA have type 2 diabetes [33–37]. The evidence for type 2 diabetes in these patients include obesity, family history of diabetes, relatively preserved insulin secretion, low prevalence of beta cell autoimmunity, and the ability to discontinue insulin therapy during the period of near-normoglycemia [38–40].