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Review

Defining and characterising diabetic ketoacidosis in adults

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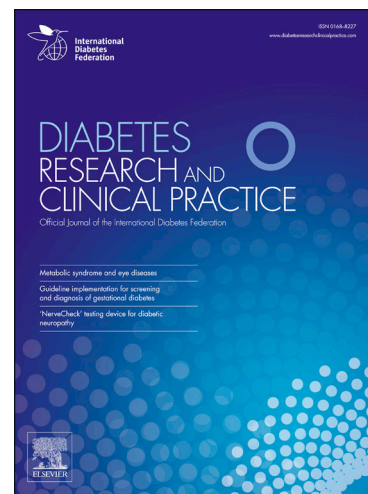
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Title: Defining and characterising diabetic ketoacidosis in adults

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Abstract**Aims**

Diabetic ketoacidosis (DKA) remains one of the most frequently encountered diabetes related emergencies, and despite updates in management and increasing standardisation of care, still has an appreciable morbidity and mortality. This review focusses on the pathophysiology and epidemiology of DKA, but also on the importance of having a standardised definition.

Methods

Relevant data were reviewed where there was available basic science or clinical papers published in peer-reviewed international journals on DKA. These included consensus documents and national or international guidelines

Results

The prevalence of DKA varies around the world, but part of this could be down to the way the condition is defined. Examples of this difference include the recent studies on sodium glucose co-transporter inhibitors in people with type 1 and type 2 diabetes which have all been associated with increased rates of DKA, but have highlighted how differences in definitions can make comparisons between agents very difficult.

Conclusions.

DKA should only be diagnosed when all three components are present – the 'D', the 'K' and the 'A'. In addition, the definitions used to diagnose DKA should be standardised – in particular for clinical trials.

Introduction

Diabetic ketoacidosis (DKA) occurs most commonly as a result of absolute or relative insulin deficiency and remains one of the most frequent causes of death in children and young adults with type 1 diabetes. Whilst DKA occurs most frequently in those with type 1 diabetes, it can occur in people with type 2 diabetes or gestational diabetes. There has been a resurgence of interest in DKA over the last few years due to it developing with increased frequency in people taking sodium glucose co-transporter (SGLT) inhibitors. In particular, recently published trials using these agents in people with type 1 diabetes have shown a significant risk of developing DKA. Thus there is a pressing need to be able to diagnose and treat this condition appropriately. To date, however, direct comparisons of the how frequently DKA develops using a particular agent has proved impossible because the trials all used different definitions.

Pathophysiology

Depending on the circulating concentration, insulin has several effects; at the very lowest concentrations, insulin inhibits lipolysis and thus switches off ketone production. At increasingly higher concentrations insulin stimulates the uptake of glucose into the cells, inhibits glycogenolysis and stimulates glycogen synthesis [1].

Thus if insulin is absent, or if concentrations of counter-regulatory hormones – cortisol, catecholamines or glucagon – are high, such as at times of acute illness, then insulin mediated cellular glucose uptake is reduced, necessitating the provision of an alternative energy substrate.

Insulin deficiency results in an increase in the activity of hormone sensitive lipase. This leads to triglyceride breakdown and free fatty acid liberation [2]. These free fatty acids form acetyl coenzyme A (CoA) due to beta oxidation, and enter the tricarboxylic acid (TCA) cycle. However, when free fatty acid concentrations are high, as with insulin deficient states, then the TCA cycle is overwhelmed and the acetyl CoA is instead converted to ketone bodies in the liver [3]. These ketone bodies enter the circulation primarily as β -hydroxybutyrate (which is, strictly speaking, a hydroxyl acid but referred to from here on as a ketone body) and acetoacetate at an approximate ratio of 10:1 [4]. Figure 1 illustrates how the raised concentration of free fatty acids due to increased lipolysis leads to a rise in CoA concentrations, which then acts as the precursor for hepatic production of beta-hydroxybutyrate, acetoacetate, and acetone.

In the clinical setting, the accumulation of these ketone bodies results in the high anion gap metabolic acidosis seen in DKA, but it is important to ensure that the high anion gap is not due to other causes of 'fixed acid' retention – e.g. ethylene glycol or methanol ingestion, lactate or 5-oxoproline accumulation, aspirin overdose, rhabdomyolysis, renal failure and ketoacidosis from other causes, e.g. liver disease.

Causes of DKA

The most common causes of this potentially life threatening condition are infection, intercurrent illness, poor adherence to prescribed medications and failure of technology, e.g. pump malfunction or faulty injection device [5,6]. Most cases occur in those with type 1 diabetes, but in some regions DKA in people type 2 diabetes accounts for up to 50% of cases, depending on family history and ethnicity [7,8].

Other reports suggest that it is fragmentation of care, and lack of continuity that contribute to episodes of recurrent DKA – and increased DKA associated mortality [9]. Other factors contributing to recurrent admissions were the presence of co-morbidities, such as end stage renal failure, drug or alcohol misuse, non-concordance with insulin therapy, mental health disorders and discharge against medical advice [10,11]. Over 40% of cases may be readmitted within 2 weeks of discharge [10].

Previous work has suggested that DKA in adults is the presenting feature in up to 30% of new cases of type 1 diabetes [12-17], but this may be as high as 80% for children [18]. Recent data from the UK suggests that in adults, 30% may be an overestimate, with a new diagnosis of type 1 diabetes only occurring in 3-6% of cases [6,19].

Epidemiology – prevalence, mortality and cost

The prevalence of DKA also varies across the world. In North America, the most recent data from the type 1 diabetes exchange registry suggests that - for those looked after in specialist centres - the rate is 3% every 3 months [20]. This is in contrast to previous data suggesting rates between 1% and 5%, equating to 145,000 cases per year [12,21]. More recent figures from the US Department of Health and Human Services / Centers for Disease Control and Prevention suggest that between 2009 and 2014 the rates of DKA rose from 19.5 to 30.2 per 1000 patient years with no clear explanation why this may be the case [22]. In the UK the reported rates are about 3.6%, equating to 48 episodes per 1000 patient years [23], similar to previous data from elsewhere in Northern Europe [24-26]. Data from the UK suggested that

rates of hospital admission with DKA have risen between 1997 and 2013 [27]. For those with type 1 diabetes there was a marked rise starting in 2004 rising from approximately 28 per 1000 patient years, to approximately 43 per 1000 patient years by 2007 – an annual percentage change of 14.1, whereas for those with type 2 diabetes, there has been a steady rise in incidence from 1997 to 2013 from 0.6 to 1.0 per 1000 patient years, an annual percentage change of 4.24 [27]. However, more recent data from Germany suggests that overall rates have decreased slightly to 25 per 1000 patient years, with the highest rates in those aged 18-30 years old [28]. Rates are reported to be much higher in the Western Pacific at 100 per 1000 patient years in children [29]. Recent work has suggested that in children and adolescent, there is a relationship between the development of DKA and a country's level of development, i.e. the highest rates occur in least developed nations [30].

Mortality in DKA varies across the world. In the US, data from the Centres for Disease Control and others suggest that mortality declined between 2000 and 2014 from 1.1% to 0.4% whilst in the UK, mortality has also been reported at <1% [6,22,31,32]. In India however in-hospital mortality may be as high as 30% [33].

Treatment of DKA is expensive, with costs in the USA estimated to be in the region of \$26,566 per episode [32], but in the UK this is £2,064 for adults and £1,387 in adolescents [34,35]. These costs are relevant, because in those health economies where the individual has to pay for their own care, treatment regimens may vary according to biochemical and clinical severity. An example of this is the United States, where some cases of 'mild' DKA may be treated as an outpatient using subcutaneous insulin regimens [36,37].

Definition

In the UK, the diagnosis of DKA in adults requires all three components to be present. The 'D' – means that the individual must have either a glucose concentration of $>200\text{mg/dl}$ (11.1mmol/l) at the time of presentation, or have been previously diagnosed with diabetes. The 'K' means they must have plasma beta-hydroxybutyrate concentrations of $\geq 3.0\text{mmol/l}$, or urine ketones of more than 2+ on a standard urine ketone stick. The 'A' means they must have a $\text{pH} < 7.3$ or a serum bicarbonate of $< 15.0\text{mmol/l}$ [38]. This definition is very similar to that advocated by the International Society of Pediatric and Adolescent Diabetes (ISPAD) [39]. The threshold ketone concentration of $> 3.0\text{mmol/l}$ came from a small study of 20 people, of whom 14 had presented with DKA. In their analysis of the β -hydroxybutyrate concentrations on admission, they worked out that concentrations of $< 1.0\text{mmol/l}$ were not associated with the development of DKA, those between 1.0 and $< 3.0\text{mmol/l}$ required repeated monitoring and those who had a ketone concentration of $\geq 3.0\text{mmol/l}$ required medical attention [40]. These data may no longer be up to date, and further work is needed to ensure they are correct.

The UK definition is different from that advocated in 2009 by the American Diabetes Association (ADA) [41]. However, there have been recent calls for the ADA guideline to be updated because it is no longer felt to be fit for purpose, in particular with the increased incidence of euglycaemic DKA seen with the use of the sodium glucose co-transporter (SGLT) inhibitors [42,43]. The 2009 ADA guideline starts by stating that to diagnose DKA, the glucose must be $\geq 250\text{mg/dl}$ (13.9mmol/l). More recently, however, there has been recognition that the ADA definition was no longer

appropriate, and a joint consensus document from a number of organisations including the ADA, American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the Endocrine Society, Juvenile Diabetes Research Foundation, Pediatric Endocrine Society, and the T1D Exchange suggested that a new definition be adopted [44]. This stated that DKA be diagnosed when urine or serum ketone concentrations were above the upper limit of the reference range, and when bicarbonate concentrations were $<15\text{mmol/l}$ or a pH <7.3 . Glucose is not part of their diagnostic criteria. However, this definition is potentially contentious because an anion gap is not included and thus does not account for an acidosis due to other causes. In addition, if the upper limit of ketones is 0.6mmol/l , any higher values could potentially lead to an over-diagnosis of DKA [44].

Further data are emerging from several sources suggesting that significant numbers of people presenting with DKA whilst taking SGLT inhibitors - 71% according to the Food and Drug Administration (FDA) Adverse Event Reporting System - present with a glucose concentration between $150\text{-}250\text{mg/dl}$ ($8.3\text{-}13.9\text{mmol/l}$) – a condition known as euglycaemic DKA. Therefore these criteria clearly need revising [45-48].

Measurement of ketones

Blood ketone concentrations should be monitored in preference to urinary ketones. The reasons for this are discussed in detail elsewhere [49], but include that the predominant ketone in the blood is β -hydroxybutyrate whilst the predominant ketone in the urine is its breakdown product, acetoacetate. Thus, measuring only urine will give a false reading as to the time taken to achieve biochemical resolution. In

addition, ketones in the urine only become apparent when urine is passed, and in a person who is dehydrated, this may be several hours [49].

Euglycaemic DKA

This condition was first described in 1973 where the authors described how 17.5% of 211 people presenting with DKA had an initial glucose concentration at presentation of <300mg/dl (16.7mmol/l) [50]. Twenty years later, another group of authors reported that in 722 episodes of DKA, 3.2% has euglycaemic DKA using the same glucose threshold, but this dropped to 0.8-1.1% if the glucose cut-off value was 180mg/dl (10.0mmol/l) [51]. The current ADA guidelines cite a further reference, and quote a prevalence of 10% for those presenting with a glucose of <250mg/dl (13.9mmol/l) [41,52]. Data from a national and local survey carried out in 2014 and 2015 in the UK (i.e. prior to the widespread use of SGLT inhibitors) suggest that in adults, the rates of euglycaemic DKA were 3%, 5.4% and 8.7% when using admission glucose thresholds of <200mg/dl (11.0mmol/l), <250mg/dl (13.9mmol/l), and <300mg/dl (16.7mmol/l) respectively [6,53,54].

The pathogenesis of euglycaemic DKA is thought to be somewhat different to hyperglycaemic DKA, with a lesser degree of insulin deficiency/resistance leading to lower excess glucose production and higher glucose disposal. There are data to suggest that renal glucose clearance is higher in this condition than with hyperglycaemic DKA [55]. Euglycaemic DKA can occur in a number of other conditions such as pregnancy, where the foeto-placental unit utilises glucose leading to lowered insulin requirement. This leads to higher free fatty acid production thus leading to ketosis in the presence of low glucose. Physiological ketonaemia occurs in

starvation or decreased carbohydrate intake, but an inability to produce endogenous carbohydrate, e.g. with glycogen storage disease or inborn errors of metabolism, alcoholism, or severe liver disease can also lead to high ketone concentrations. These conditions are considered in more detail elsewhere [56].

Given the lower glucose in euglycaemic DKA, the only major difference in treatment would be the earlier use of a dextrose containing fluid as the substrate for the insulin infusion in addition to the 0.9% sodium chloride solution given as the resuscitation fluid.

SGLT inhibitor use and DKA

The use of these agents is undoubtedly associated with an increased risk of developing DKA, even in those with type 2 diabetes [45-48]. In the trials using SGLT inhibitors in people with type 1 diabetes, the reported rates of DKA were much higher in the drug arms than for those in the placebo arms. For those on empagliflozin 2.5mg the rate was 0.8%, on 10mg it was 4.3%, and for 25mg it was 3.3%, compared to a rate on placebo of 1.2%, equating to rates of 59.4, 50.5 and 17.7 events per 1000 patient years respectively [57]. The rates for dapagliflozin was 2.6% or 4% on 5mg (58.3 or 47.6 events per 1000 patient years), on 10mg the rates were 2.2% or 3.4% (49.9 or 36.7 events per 1000 patient years), compared with rates of up to 1.9% on placebo (21.5 events per 1000 patient years) [47,58]. For sotagliflozin 200mg the rates were 2.3% or 3.4%, and for the 400mg dose, the rates were 3.0% or 3.4% (30 or 34 events per 1000 patient years), compared with rates on placebo of 0.0%-0.6% (0 to 3.8 events per 1000 patient years) [59-62]. These episodes occurred despite the robust risk mitigation strategies in place. The lower rates in the

placebo arms of the trials compared to previously published rates suggested that these risk mitigation strategies worked. However despite these being in place, DKA occurred 2.3 – 5.6 times more frequently with the use of the SGLT inhibitors. If one were to extrapolate the rates to that seen in the 'real-world' literature where the risk mitigation may not be as rigorously enforced, then the argument against their use is that DKA rates may increase to between approximately 140 and 270 cases per 1000 patient years in adults. As an illustration, in their analysis of the data submitted for sotagliflozin approval, the US FDA calculated the number needed to harm of between 205 and 311 per 1000 patient years [48]. Whilst the FDA issued a complete response letter for sotagliflozin, indicating that the drug cannot be approved in its current form [63], in January 2019 the European Medicines Agency recommended a change to the terms of the marketing authorization for dapagliflozin allowing it to be used as an “adjunct to insulin in patients with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy” [64]. The impact of this decision remains uncertain given the increased DKA risk.

One of the main concerns with the incidence data however, is that there has been no standardised definition used across clinical trials where DKA was a clinical risk. This makes direct comparison of DKA incidence rates between agents impossible [47,57,60,61]. This is illustrated by the DKA data from the canagliflozin studies where the investigators reported 12 cases of DKA across their trial programme [65]. However, their data has been criticised because of their twelve cases of 'DKA' 1 did not have a glucose, 6 did not have a pH, 5 did not have a bicarbonate measurement, 10 did not have an anion gap and 7 did not have ketones measured [66].

The empagliflozin study used a wide variety of 'a priori' definitions [57]. The authors suggested that DKA was certainly present if the pH was ≤ 7.3 and blood β -hydroxybutyrate of $> 1.5 \text{ mmol/l}$ and urine ketones ' $\geq ++$ '. It was also present even if the pH was unavailable but the bicarbonate was $< 15.0 \text{ mmol/l}$, blood β -hydroxybutyrate of $> 1.5 \text{ mmol/l}$ and urine ketones ' $\geq ++$ '. The authors described ++ or +++ urine ketones as 'moderate' or 'large', translating to a blood β -hydroxybutyrate concentration of $1.5\text{-}2.9 \text{ mmol/l}$. ++++ urinary ketones was described as 'very large', and equivalent to $\geq 3.0 \text{ mmol/l}$ of β -hydroxybutyrate. Cases were described as 'potential DKA' if the pH was ≤ 7.3 , with a suggestive history (e.g. pump failure, missed insulin doses, intercurrent illness, incorrect implementation of sick day rules, etc.). Alternatively pH was ≤ 7.3 and typical symptoms were also present, then this could also be defined as 'potential DKA'. Such symptoms included confusion, reduced conscious level or drowsiness, dehydration, Kussmaul breathing, abdominal pain, nausea or vomiting. Potential DKA was also defined if the pH were not available, but the bicarbonate was $\leq 18.0 \text{ mmol/l}$, and suggestive signs or symptoms were present, or if the serum bicarbonate was $15.0\text{-}18.0 \text{ mmol/l}$, together with blood β -hydroxybutyrate concentration of $> 1.5 \text{ mmol/l}$ with urinary ketones of $\geq ++$. In this combination, signs and symptoms were not necessary, unlike if the pH or bicarbonate were unavailable, but the blood β -hydroxybutyrate concentration was > 1.5 and urinary ketones were $\geq ++$. The final 'potential DKA' category was no pH, no bicarbonate, but a blood β -hydroxybutyrate concentration of $> 3.8 \text{ mmol/l}$ with urinary ketones of ++++.

The cases that were adjudicated as 'unlikely DKA' had a blood β -hydroxybutyrate concentration of ≤ 1.5 mmol/l and/or a pH > 7.3 , or if the pH was unavailable, a bicarbonate concentration of > 18.0 mmol/l. Those individuals who had a blood β -hydroxybutyrate concentration of > 1.5 and < 3.8 mmol/l and a pH > 7.3 , or a bicarbonate of > 18.0 mmol/l if the pH was unavailable, were classified as 'unlikely DKA but ketosis'. If only a pH of ≤ 7.3 , or a bicarbonate of ≤ 18.0 mmol/l or only symptoms or signs were present then they were 'unclassifiable'.

The dapagliflozin studies used the ADA guideline [41] "but without the requirement for hyperglycaemia" [58]. The sotagliflozin studies definition was based on the ADA guideline [41] - i.e. "anion-gap metabolic acidosis related to excessive ketone production without a satisfactory alternative cause for anion-gap acidosis". They went on to say that "However, final diagnosis of metabolic acidosis, including diabetic ketoacidosis, was made by the adjudication committee." [59]. Furthermore, the adjudication committee classified the events as "Yes, with certainty", "Yes, probably", "No, unlikely", "No, with certainty", "Unclassifiable", or "Insufficient data". [60].

These definitions were all subtly different from the – relatively straightforward – UK guideline from the Joint British Diabetes Societies which is also widely used, i.e. ketonaemia > 3.0 mmol/l **or** significant ketonuria (more than 2+ on standard urine sticks) **AND**, a blood glucose > 11.0 mmol/l (200mg/dl) or known diabetes mellitus **AND** a bicarbonate (HCO_3^-) < 15.0 mmol/l **and/or** venous pH < 7.3 [38].

The definition of DKA needs to be standardized

What these trials show is the heterogeneity surrounding definitions. Not only that, what access different institutions have to the tests used to diagnose DKA needs to be consistent. There has been a previous call to standardise the definition of DKA to avoid the current – confusing – situation [43]. But to allow the definitions to be standardised, there needs to be an agreement on what criteria to use – especially in the clinical trial setting. A blood gas analyser is a common finding in many hospitals, thus the 'D', the 'K' and the 'A' need to be measured in order to make a diagnosis. A capillary (or plasma) glucose should be readily available. A blood β -hydroxybutyrate concentration – either bedside using a point of care meter, or laboratory measurement should be taken. A previous review has described the disadvantages of using urine ketones in the management of DKA [49]. A venous (not arterial) pH and bicarbonate measurement should be the minimum standard that pharmaceutical companies and others should insist on being measured when DKA is suspected because the differences between arterial and venous values are not significantly different enough to affect patient management [67,68]. In addition, the anion gap should be high, with no other attributable cause. The anion gap is a relatively easy calculation from standard blood tests of renal function ($[\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$) – the potassium can be added to the anion side of the equation, but is often not high enough to affect an individuals' management. However, the need to identify a high anion gap means that chloride measurement needs to be available. Indeed, trial sites should only be used when these facilities and measurements are routinely available.

It is acknowledged however, that filling these diagnostic gaps remains aspirational, because there are little data to suggest that not having them is associated with harm. However, for centres involved in clinical trials these should be mandatory.

Clinical context

For many clinicians treating DKA 'at the front door' the subtleties of a standard definition for DKA may be lost – the simple message of ensuring DKA is diagnosed when someone has a raised glucose (or a history of diabetes), a raised ketone concentration and an acidosis should prompt urgent treatment. In addition, other situations, such as euglycaemic DKA or keto-alkalosis following excessive vomiting should be recognised and treated. What remains unknown however, is does using these very small differences in definitions lead to different outcomes. As always, treating with fluids, insulin and electrolyte replacement and ensuring patient safety comes first.

In Summary

Prior to the discovery of insulin in 1921, type 1 diabetes was universally fatal, most frequently due to DKA. Even with the many advances in care over the last few decades there remain many challenges in the management of this condition. Whilst the principles of treatment remain unchanged with fluids, insulin and electrolyte replacement, DKA still has an appreciable mortality in many parts of the world. Key to managing the condition starts with the correct diagnosis. Despite increasing recognition of DKA, in particular with the use of the SGLT inhibitors, we still do not have unified diagnostic criteria that can be used. This needs to be urgently addressed.

References

- [1] Barwell ND, McKay GA, Fisher M. Drugs for diabetes: part 7 insulin. *Br J Cardiol* 2011; **18**:224-228.
- [2] Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. *N Eng J Med* 1983; **309**(3):159-169.
- [3] McGarry JD, Woeltje KF, Kuwajima M, Foster DW. Regulation of ketogenesis and the renaissance of carnitine palmitoyltransferase. *Diabetes Metab Rev* 1989; **5**(3):271-284.
- [4] Stentz FB, Umpierrez GE, Cuervo R, Kitabchi AE. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. *Diabetes* 2004; **53**(8):2079-2086.
- [5] Umpierrez G, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. *Nat Rev Endocrinol* 2016; **12**(4):222-232.
- [6] Dhatariya KK, Nunney I, Higgins K, Sampson MJ, Iceton G. A national survey of the management of diabetic ketoacidosis in the UK in 2014. *Diabetic Med* 2016; **33**(2):252-260.
- [7] Wang ZH, Kihl-Selstam E, Eriksson JW. Ketoacidosis occurs in both Type 1 and Type 2 diabetes— a population-based study from Northern Sweden. *Diabetic Med* 2008; **25**(7):867-870.

- [8] Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: Ketosis-prone type 2 diabetes mellitus. *Ann Intern Med* 2006; **144**(5):350-357.
- [9] Mays JA, Jackson KL, Derby TA *et al.* An evaluation of recurrent diabetic ketoacidosis, fragmentation of care, and mortality across Chicago, Illinois. *Diabetes Care* 2016; **39**(10):1671.
- [10] Hurtado CR, Lemor A, Vallejo F *et al.* Causes and predictors for 30-day re-admissions in adult patients with diabetic ketoacidosis in the United States: A nationwide analysis, 210-2014. *Endocr Pract* 2019; **25**(3):242-253.
- [11] Del Degan S, Dube F, Gagnon C, Boulet G. Risk factors of recurrent diabetic ketoacidosis in adults with type 1 diabetes. *Can J Diabetes* 2019.
- [12] Faich GA, Fishbein HA, Ellis SE. The epidemiology of diabetic acidosis: a population-based study. *Am J Epidemiol* 1983; **117**(5):551-558.
- [13] Ellemann K, Soerensen JN, Pedersen L, Edsberg B, Andersen OO. Epidemiology and treatment of diabetic ketoacidosis in a community population. *Diabetes Care* 1984; **7**(6):528-532.
- [14] Bui TP, Werther GA, Cameron FJ. Trends in diabetic ketoacidosis in childhood and adolescence: a 15-yr experience. *Pediatr Diabetes* 2002; **3**(2):82-88.
- [15] Dunger DB, Sperling MA, Acerini CL *et al.* European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society Consensus Statement on diabetic ketoacidosis in children and adolescents. *Pediatrics* 2004; **113**(2):e133-e140.

- [16] Rewers A, Dong F, Slover RH, Klingensmith G, Rewers M. Incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado youth, 1998-2012. *JAMA* 2015; **313**(15):1570-1572.
- [17] Usher-Smith JA, Thompson M, Ercole A, Walter FM. Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review. *Diabetologia* 2012; **55**(11):2878-2894.
- [18] Jefferies CA, Nakhla M, Derraik JG *et al.* Preventing diabetic ketoacidosis. *Pediatric Clinics* 2015; **62**(4):857-871.
- [19] Edge JA, Nunney I, Dhatariya KK. Diabetic ketoacidosis in an adolescent and young adult population in the UK in 2014: a national survey comparison of management in paediatric and adult settings. *Diabetic Med* 2016; **33**(10):1352-1359.
- [20] Foster NC, Beck RW, Miller KM *et al.* State of type 1 diabetes management and outcomes from the T1D Exchange in 2016-2018. *Diabetes Technol Ther* 2019; **21**(2):66-72.
- [21] Ginde AA, Pelletier AJ, Camargo CA. National study of U.S. emergency department visits with diabetic ketoacidosis, 1993-2003. *Diabetes Care* 2006; **29**(9):2117-2119.
- [22] Benoit SR, Zhang Y, Geiss LS, Gregg EW, Albright A. Trends in diabetic ketoacidosis hospitalizations and in-hospital mortality - United States, 2000-2014. *Morb Mortal Wkly Rep* 2018; **67**:362-365.

- [23] Health and Social Care Information Centre. National Diabetes Audit 2012-2013. Report 2: Complications and Mortality. <https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/national-diabetes-audit-2012-2013-report-2>. 2015. [Last accessed 21st June 2019]
- [24] Karges B, Rosenbauer J, Holterhus PM *et al*. Hospital admission for diabetic ketoacidosis or severe hypoglycemia in 31,330 young patients with type 1 diabetes. *Eur J Endocrinol* 2015; **173**(3):341-350.
- [25] Henriksen OM, Roder ME, PrahJ JB, Svendsen OL. Diabetic ketoacidosis in Denmark. *Diabetes Res Clin Pract* 2007; **76**(1):51-56.
- [26] Rosilio M, Cotton JB, Wieliczko MC *et al*. Factors associated with glycemic control: A cross-sectional nationwide study in 2,579 French children with type 1 diabetes. *Diabetes Care* 1998; **21**(7):1146-1153.
- [27] Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998-2013: A retrospective cohort study. *Diabetes Care* 2018; **41**(9):1870-1877.
- [28] Kalscheuer H, Seufert J, Lanzinger S *et al*. Event rates and risk factors for the development of diabetic ketoacidosis in adult patients with type 1 diabetes: Analysis from the DPV registry based on 46,966 patients. *Diabetes Care* 2019;dc181160.
- [29] Craig ME, Jones TW, Silink M, Ping YJ. Diabetes care, glycemic control, and complications in children with type 1 diabetes from Asia and the Western Pacific Region. *J Diabetes Complications* 2016; **21**(5):280-287.

- [30] Große J, Hornstein H, Manuwald U *et al.* Incidence of diabetic ketoacidosis of new-onset type 1 diabetes in children and adolescents in different countries correlates with human development index (HDI): An updated systematic review, meta-analysis, and meta-regression. *Horm Metab Res* 2018; **50**(3):209-222.
- [31] Gibb FW, Teoh WL, Graham J, Lockman KA. Risk of death following admission to a UK hospital with diabetic ketoacidosis. *Diabetologia* 2016; **59**(10):2082-2087.
- [32] Desai D, Mehta D, Mathias P, Menon G, Schubart UK. Health care utilization and burden of diabetic ketoacidosis in the U.S. over the past decade: A nationwide analysis. *Diabetes Care* 2018; **41**(8):1631-1638.
- [33] Agarwal A, Yadav A, Gutch M *et al.* Prognostic factors in patients hospitalized with diabetic ketoacidosis. *Endocrinol Metab* 2016; **31**(3):424-432.
- [34] Dhatariya KK, Skedgel C, Fordham R. The cost of treating diabetic ketoacidosis in the UK: a national survey of hospital resource use. *Diabetic Med* 2017; **34**(10):1361-1366.
- [35] Dhatariya KK, Parsekar K, Skedgel C *et al.* The cost of treating diabetic ketoacidosis in an adolescent population in the UK: a national survey of hospital resource use. *Diabetic Med* 2019; DOI: 10.1111/dme.13893
- [36] Umpierrez GE, Cuervo R, Karabell A *et al.* Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. *Diabetes Care* 2004; **27**(8):1873-1878.

- [37] Fisher JN, Shahshahani MN, Kitabchi AE. Diabetic ketoacidosis: low-dose insulin therapy by various routes. *N Eng J Med* 1977; **297**(5):238-241.
- [38] Savage MW, Dhatariya KK, Kilvert A *et al.* Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. *Diabetic Med* 2011; **28**(5):508-515.
- [39] Wolfsdorf JI, Glaser N, Agus M *et al.* ISPAD clinical practice consensus guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes* 2018; **19**(S27):155-177.
- [40] Wallace TM, Meston NM, Gardner SG, Matthews DR. The hospital and home use of a 30-second hand-held blood ketone meter: guidelines for clinical practice. *Diabetic Med* 2001; **18**(8):640-645.
- [41] Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; **32**(7):1335-1343.
- [42] Dhatariya KK, Umpierrez GE. Guidelines for management of diabetic ketoacidosis: time to revise? *Lancet Diabetes Endocrinol* 2017; **5**(5):321-323.
- [43] Dhatariya KK. Why the definitions used to diagnose diabetic ketoacidosis should be standardised. *Diabetes Res Clin Pract* 2018; **135**:227-228.
- [44] Agiostratidou G, Anhalt H, Ball D *et al.* Standardizing clinically meaningful outcome measures beyond HbA1c for type 1 diabetes: A consensus report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley

Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange.

Diabetes Care 2017; **40**(12):1622-1630.

- [45] Peters AL, Buschur EO, Buse JB *et al.* Euglycemic diabetic ketoacidosis: A potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care* 2015; **38**(9):1687-1693.
- [46] Blau JE, Tella SH, Taylor SI, Rother KI. Ketoacidosis associated with SGLT2 inhibitor treatment: Analysis of FAERS data. *Diabetes Metab Res Rev* 2017; **33**(8):e2924-e2n/a.
- [47] Dandona P, Mathieu C, Phillip M *et al.* Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: The DEPICT-1 52-week study. *Diabetes Care* 2018; **41**(12):2552-2559.
- [48] US Food and Drug Administration. FDA briefing document. Endocrinologic and metabolic drugs advisory committee meeting 17th January 2019. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM629485.pdf>. 2019. [Last accessed 21st June 2019]
- [49] Dhatariya K. Blood ketones - measurement, interpretation, limitations and utility in the management of diabetic ketoacidosis. *Rev Diabet Stud* 2016; **13**(4):217-225.
- [50] Munro JF, Campbell IW, McCuish AC, Duncan JP. Euglycaemic diabetic ketoacidosis. *Br Med J* 1973; **2**(5866):578-580.

- [51] Jenkins D, Close CF, Krentz AJ, Natrass M, Wright AD. Euglycaemic diabetic ketoacidosis: does it exist? *Acta Diabetol* 1993; **30**(4):251-253.
- [52] Miles JM, Gerich JE. Glucose and ketone body kinetics in diabetic ketoacidosis. *Clin Endocrinol Meta* 1983; **12**(2):303-319.
- [53] Varadarajan M, Patel M, Kakkar N *et al.* Are the results from the 2014 UK national survey on the management of diabetic ketoacidosis applicable to individual centres? *Diabetes Res Clin Pract* 2017; **127**:140-146.
- [54] Macfarlane J, Dhatariya K. The incidence of euglycemic diabetic ketoacidosis in adults with type 1 diabetes in the UK prior to the widespread use of sodium glucose co-transporter 2 inhibitors. *Mayo Clin Proc* 2019. [Accepted for publication]
- [55] Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: A predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care* 2015; **38**(9):1638-1642.
- [56] Barski L, Eshkoli T, Brandstaetter E, Jotkowitz A. Euglycemic diabetic ketoacidosis. *Eur J Intern Med* 2019; **63**:9-14.
- [57] Rosenstock J, Marquard J, Laffel LM *et al.* Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: The EASE trials. *Diabetes Care* 2018; **41**(12):2560-2569.
- [58] Mathieu C, Dandona P, Gillard P *et al.* Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 Study):

- 24-week results from a randomized controlled trial. *Diabetes Care* 2018; **41**(9):1938-1946.
- [59] Garg SK, Henry RR, Banks P *et al.* Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Eng J Med* 2017; **377**(24):2337-2348.
- [60] Buse JB, Garg SK, Rosenstock J *et al.* Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: The North American inTandem1 study. *Diabetes Care* 2018; **41**(9):1970-1980.
- [61] Danne T, Cariou B, Banks P *et al.* HbA1c and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: The European inTandem2 study. *Diabetes Care* 2018; **41**(9):1981-1990.
- [62] Musso G, Gambino R, Cassader M, Paschetta E. Efficacy and safety of dual SGLT 1/2 inhibitor sotagliflozin in type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2019; **365**:l1328.
- [63] Wall Street Journal. FDA rejects oral treatment for type 1 diabetes. <https://www.wsj.com/articles/fda-rejects-oral-treatment-for-type-1-diabetes-11553282012>. 22-3-2019. [Last accessed 21st June 2019]
- [64] European Medicines Agency. Forxiga. <https://www.ema.europa.eu/en/medicines/human/summaries-opinion/forxiga> . 2019. [Last accessed 21st June 2019]

- [65] Erondy N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. *Diabetes Care* 2015; **38**(9):1680-1686.
- [66] Dhatariya K. Comment on Erondy N et al – Does this data significantly underestimate the prevalence of SGLT-2 associated DKA? *Diabetes Care* 2016; **39**(1):e18.
- [67] Ma OJ, Rush MD, Godfrey MM, Gaddis G. Arterial blood gas results rarely influence emergency physician management of patients with suspected diabetic ketoacidosis. *Acad Emerg Med* 2003; **10**(8):836-841.
- [68] Herrington WG, Nye HJ, Hammersley MS, Watkinson PJ. Are arterial and venous samples clinically equivalent for the estimation of pH, serum bicarbonate and potassium concentration in critically ill patients? *Diabetic Med* 2012; **29**(1):32-35.

Legends

Figure 1. A simplified illustration showing the metabolic pathway for

ketogenesis. During insulin deficiency, glucose uptake into cells is limited, and there is a need for an alternative energy substrate. The breakdown of non-esterified fatty acids allows the entry of fatty acid CoA to enter the tricarboxylic acid cycle, thus generating ATP. However, excess fatty acid CoA production leads to the production of acetoacetate (a ketoacid) and beta-hydroxybutyrate (a hydroxyl-acid), causing ketoacidosis in periods of extended insulin deficiency. From reference [49].

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