problems associated with the interpretation of office blood pressure data when different methods are used.

Until then, we would like to make a plea to the SPRINT investigators to publish trial data on cardiovascular outcomes in patients that developed diabetes during the course of the study, because we think that many of the high-risk patients involved were in the pre-diabetes range.

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Guidelines for management of diabetic ketoacidosis: time to revise?

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Guidelines and position statements from medical organisations are widely used by clinicians to guide the care of their patients. The 2009 American Diabetes Association (ADA) position statement on hyperglycaemic emergencies in adult patients with diabetes details the management of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemia state.[1] The guideline is used internationally and has been cited more than 600 times. Part of the reason for this high level of use might be because of the lack of national guidelines in other countries. However, a great deal of new evidence has emerged since its publication—as such, a revision of the position statement is now necessary.

The current ADA diagnostic criteria for DKA are a glucose concentration greater than 13·9 mmol/L (250 mg/dL; the 'D' of DKA), the presence of ketones (in urine or in the blood; the 'K'), and the occurrence of metabolic acidosis (the 'A'), with a pH of less than 7·30 (measured in arterial or venous blood) and a serum bicarbonate concentration of 18·0 mmol/L or lower. DKA is often misdiagnosed, with some patients' diagnosis being based on clinical history alone, or more often on the basis of urine ketones being present in a patient with diabetes who is unwell, without further biochemical confirmation.

The ADA guideline suggests a glucose concentration cutoff of 13·9 mmol/L (250 mg/dL) or higher to make the diagnosis of DKA; however, many patients present with smaller increases in plasma glucose concentration after withholding or decreasing their insulin dose in the presence of illness or reduced food intake.[2] In 1973, Munro and colleagues[2] reported that among 211 episodes of DKA, 16 (7·6%) had a blood glucose

concentration lower than 11·1 mmol/L (200 mg/dL), a condition which has been referred to as euglycaemic DKA. This presentation is also seen in pregnant women with diabetes, patients with impaired gluconeogenesis due to alcohol abuse, and, more recently, in patients treated with SGLT2 inhibitors.[1,3] Because these disparate conditions require different treatments, a thorough history must be taken to ensure that euglycaemic DKA is not missed. We propose that the glycaemic criteria for diagnosis should be changed to a blood glucose concentration of 11·1 mmol/L (200 mg/dL) or higher.

The key diagnostic laboratory feature of DKA is the increase in circulating ketone concentrations. However, high ketone concentrations can also occur in patients with chronic alcohol intake with a recent binge (alcoholic ketoacidosis), nausea, and vomiting.[4] The assessment of augmented ketonaemia is done by direct measurement of β-hydroxybutyrate (a hydroxy acid) and by the nitroprusside reaction in plasma or urine. The nitroprusside reaction provides a semi-quantitative estimation of acetoacetate (a ketoacid), but does not detect the presence of β-hydroxybutyrate, which is the predominant ketone body.[5] In urine, acetoacetate is the major ketone;[6] however, the urine test does not reflect the concentration of plasma β-hydroxybutyrate. Additionally, as DKA resolves, β-hydroxybutyrate is converted into acetoacetic acid, which is then renally excreted. This sequence leads to the false impression that the DKA is taking longer to resolve than is the case.[7]

The existing ADA position statement[1] gives equal diagnostic value to increased urine acetoacetate and blood β-hydroxybutyrate. We propose that any revised guideline should state strongly that although urine ketones might be appropriate for diagnosis of DKA, direct measurement of β-hydroxybutyrate—either via a laboratory or by point-of-care testing—should be preferred both for diagnosis of ketoacidosis (≥3 mmol/L) and to assess the patient's response to treatment. Notably, measurement of blood ketones has been recommended in national guidance in the UK for assessment of response to therapy and in guiding of insulin infusion rates.[8]

Accumulation of β-hydroxybutyrate and acetoacetic acid leads to a high anion gap ($Na^+ - [Cl^- + HCO_3^-]$) metabolic acidosis. However, more than a third of patients with DKA present with mixed anion gap acidosis and hyperchloremic metabolic acidosis or develop a transient normal anion gap acidosis following a large or rapid infusion of isotonic saline.[9]

The ADA recommends[1] continuous intravenous insulin infusion as the preferred regimen for most patients with DKA, except in mild and uncomplicated cases. Most cases of moderate or severe DKA would mandate admission to an intensive care unit. In countries with low resources, or where patients need to pay for their own treatment, there is a strong argument for such a classification. Available evidence shows that in patients with mild to moderate DKA who are not peripherally hypoperfused, the use of weight-based subcutaneous or intramuscular insulin given every 1–2 h in a general ward environment offers a feasible alternative to intravenous insulin.[10] No significant differences have been identified between subcutaneous and intramuscular insulin with respect to the rate of decline of blood glucose concentration, treatment duration until resolution of ketoacidosis, total amount of insulin administered, length of hospital stay, or number of hypoglycaemic events.[10] Intravenous insulin administration should be considered in all patients with severe and complicated DKA, anasarca, severe hypoperfusion, and hypovolemic shock. However, for most patients with mild and uncomplicated DKA, we recommend greater use of subcutaneous or intramuscular insulin as an alternative to intravenous insulin.

The ADA position statement classifies DKA into mild, moderate, and severe on the basis of a combination of pH, serum bicarbonate, anion gap, and mental state.[1] The importance of increased serum osmolality in the clinical presentation and outcome of patients with DKA is well established.[11] Increased osmolality is associated with changes in sensorium (lethargy, stupor, coma), complications (cerebral oedema), and mortality.[9] Estimates suggest that about 20–30% of patients present with combined ketoacidosis and hyperosmolality.[12] We suggest that the presence of hyperosmolality (effective serum osmolality [2 × (measured Na^+ in mEq/L) + (glucose concentration in mmol/L)] >320 mmol/kg) should be considered as an important criterion in grading the severity of DKA.

Financial pressures on health systems mean that admissions avoidance and reducing the length of hospital stays are of paramount importance, while ensuring and maintaining patient safety and appropriate care. The revised guidance for DKA should therefore have an additional focus on mechanisms to

help reduce length of hospital stay. Data show that the continuation of basal insulin facilitates treatment and reduces the incidence of rebound hyperglycaemia when the variable-rate intravenous insulin infusion is being discontinued and the patient is being transferred to subcutaneous insulin.[13] This approach has been advocated in other protocols, and has been shown to reduce length of stay.[8]

In revising and updating guidelines, the target audience is an important consideration. Most DKA hospital admissions are medical emergencies, in which patients present to emergency departments where they are diagnosed and initially managed. The existing ADA position statement[1] is long, and most emergency department staff are unlikely to have read the entire text, or, if they have, they are unlikely to recall the details. Many departments might have reproduced the figure from the position statement (figure 2[1]) that outlines the steps necessary to manage these emergencies. This approach might be correct for most patients. However, how many of the emergency room staff will be familiar with the concept of euglycaemic DKA, or aware that up to 10% of patients might present with this condition?[2] How many will know of the small but important risk of SGLT2 inhibitor-associated euglycaemic DKA in people with type 1 or type 2 diabetes[3] or in pregnant women with (predominantly type 1) diabetes?[14] Thus, the issue remain one of accurate diagnosis—the legend of the widely reproduced guideline figure from the ADA position statement states "DKA diagnostic criteria: blood glucose 250 mg/dL, arterial pH 7·3, bicarbonate 15 mEq/L, and moderate ketonuria or ketonemia",[1] whereas the text (which is not often reproduced) states that these criteria might be inaccurate in roughly 10% of cases. As always, ongoing education is necessary. In future guidelines, a summary document with a clear care plan should be provided to facilitate better diagnosis and treatment.

In conclusion, we believe it is time for the ADA position statement for the management of DKA to be revised. As with the UK guideline,[8] the authors of the revised position statement should insist that the diagnosis of DKA only be made when all three criteria (the 'D', the 'K', and the 'A') are met. We advocate measurement of β-hydroxybutyrate over acetoacetate for diagnosis and assessment of response to therapy and the use of simplified treatment regimens and protocols, with the use of subcutaneous or intramuscular insulin to avoid the high cost and complexity of intravenous insulin and admission to intensive care for most patients with mild and moderate DKA. Crucially, the revised guideline needs to be aimed at those health-care staff working at the frontline in the management of patients with DKA.

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