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Why the definitions used to diagnose diabetic ketoacidosis should be standardised

Clinicians who practice evidence based medicine need to rely on good quality data to ensure the decisions they make are based on robust science. However, there is the possibility that the data currently available on the prevalence and management of diabetic ketoacidosis (DKA) relies on very flimsy trial evidence and that this potentially puts patients in danger.

Standardisation of clinic trial data is not a new thing. In the UK, work done in the early 1980s showed the methods used to measure glycated haemoglobin (HbA1c) varied greatly across the UK [1]. The investigators in the Diabetes Control and Complications (DCCT) Study also understood that the assays used in the determination of HbA1c concentrations varied across each site and each analyser [2]. They came up with the DCCT standardisation by using the National Glycohemoglobin Standardization Program (www.ngsp.org) that enabled harmonisation of the results from each site or each analyser and for these to be comparable to each other. This removed any potential sources of bias from the measurement, and thus allowed for a robust approach to the subsequent results [3]. This approach held up well until the turn of the Millennium when the need for such standardisation was removed with the use of direct measurement and the adoption of the International Federation of Clinical Chemistry methods [4].

Many national guidelines emphasise that DKA in adults and children is defined by the necessary presence of all three of these criteria. The UK national guidelines produced by the Joint British Diabetes Societies state the diagnostic criteria must include the 'D' (i.e. a personal history of diabetes mellitus or a random glucose concentration of >11.0 mmol/l [200 mg/dl]); the 'K' (i.e. the presence of a plasma β hydroxybutyrate concentration of ≥3.0 mmol/l, or significant ketonuria [more than 2 + on standard urine sticks]); and the 'A' (i.e. a pH of less than 7.3, or a serum bicarbonate concentration of <15 mmol/l) [5]. These guidelines are used by the majority of UK hospitals [6]. The American Diabetes Association (ADA) guidelines state the DKA should only be diagnosed if the glucose is >13.9 mmol/l [250 mg/dl)]; that serum or urine should be positive for ketones; and that the bicarbonate concentration be lower than 18 mmol/l [7]. The ADA also include a raised anion gap [7]. However, there has recently been a call for the ADA guidelines to be updated and revised in the face of newer information [8].

With the concerns about the potentially increased risk of DKA with the use of Sodium Glucose co-Transporter 2 (SGLT-2) inhibitors the issue about how DKA should be defined has become more important. A recent paper has suggested that the risk of developing DKA with these agents was the same as other classes of glucose lowering agents [9]. However other authors have disagreed, showing data suggesting that the risk of DKA with SGLT-2 inhibitor use is more than double that of dipeptidyl peptidase-4 (DPP4) inhibitors [10]. However, it is clear that local investigators are not using any fixed criteria to define DKA. The data looking at the incidence of DKA in the canagliflozin trials suggested that only 12 individuals developed DKA out of 17,596 patients with a mean exposure of 1.4 years [11]. Of these, 1 did not report a glucose concentration, 6 did not report a ketone concentration (and of the remainder it is recorded at '+blood' or '+urine'), 5 did not report the pH and 5 did not report a bicarbonate concentration [11]. Other data, presented in abstract form only, from the dapagliflozin trials showed that out of 915 patients, only 15.2% of people diagnosed with DKA had a glucose measured (although one assumes they all had diabetes because they were on the diabetes database or because they were in a trial for a drug used to treat type 2 diabetes), 23.8% had a ketone concentration reported (only in urine), 35.4% had a pH measured and 20.1% had a bicarbonate concentration measured [12].

It is accepted that for these trials DKA was not a prespecified adverse outcome, and thus these were not adjudicated events. These were local investigator reported events. However, these are the flawed data upon which meta-analyses are based and safety judged. None of the current analyses looking at the safety of this class of drugs look at patient level data or report how DKA was defined [10,13,14].

DKA is a potentially life threatening acute medical emergency that requires rapid diagnosis and appropriate treatment. If the condition is incorrectly diagnosed – either being diagnosed and treated when it is not truly present, or if it is missed when it is truly present – because of a lack of appropriate biochemical confirmation, then this may lead directly to harm in that individual. However, if these diagnoses are being use to make judgements about individual drugs or drug classes then there is a greater danger that drugs may been deemed safe or unsafe based on flawed data. With inhibitors of the Sodium Glucose co-Transporter being currently tested in people with type 1 diabetes, there is an urgent need to

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ensure that all clinicians use the same criteria to define and if necessary, report DKA.

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