

## Glycaemic control in diabetic ketoacidosis: too much of a good thing?

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Physiological disturbances associated with critical illness have long been compared with a “normal range” observed in healthy individuals, and hence declared in laboratory reports and bedside monitoring as “abnormal”. In parallel, clinicians using treatment options which might return the physiological values closer to the comparator range have had to consider what the goals of treatment should be. Observations that patients with fewer or less severe abnormalities were more likely to survive, and that clinical improvement was accompanied by a return of abnormal values to normal, led to the conclusion that treatments which moved the physiological state closer to “normal” were beneficial to the critically ill patient. Thus, in the early days of intensive care, treatments such as oxygen, mechanical ventilation, vasoactive infusions, fluid and electrolyte therapy, blood transfusion and diuretics were used to restore measurements of tidal volume,  $\text{PaO}_2$ ,  $\text{Paco}_2$ , mean arterial pressure, pH, haemoglobin and urine output back to close as possible to “normal”.

As it became clear that there was overt harm associated with some of these approaches, such as barotrauma in the pursuit of normocarbida, focus turned to assessing the risks versus benefits of our treatments and physiological targets. This became an increasingly nuanced approach, with effects remote from the target organ system also being considered, and eventually progressed to long-term, patient-centred outcomes. We learnt that, rather than helping our patients recover, some of our treatments and targets were reducing the prospects of a good outcome, and acceptance of some degree of “abnormality” was often required. Examples include permissive hypercarbia in acute respiratory distress syndrome,<sup>1</sup> a low haemoglobin threshold for red cell transfusion,<sup>2</sup> accepting mild hyperglycaemia,<sup>3</sup> less intensive continuous renal replacement therapy,<sup>4</sup> and a lower rather than higher blood pressure target in septic shock.<sup>5</sup>

One common critical illness with significant physiological disturbance is diabetic ketoacidosis (DKA). First described by von Stoch in 1828, this variant of diabetic coma was identified after Adolf Kussmaul noted that many patients had deep and frequent respiration, and others found high concentrations of acetoacetic acid and 3-beta-hydroxybutyric acid in the urine of these patients.<sup>6</sup> Mortality was over 90% until the discovery of insulin in 1921, but is now less than 2%.

An absolute or relative deficiency of insulin, in conjunction with an increase in counter-regulatory hormones (glucagon, cortisol, catecholamines and growth hormone), promotes hepatic gluconeogenesis and decreases peripheral insulin sensitivity, leading to hyperglycaemia. Lack of effective insulin activity enhances lipolysis in adipose tissue, breaking down triglycerides into glycerol and free fatty acids which, as part of hepatic gluconeogenesis, leads to the production of ketone bodies, primarily 3-beta-hydroxybutyrate. These strongly acidic molecules drive metabolic acidosis, and hyperglycaemia and ketonaemia lead to hyperosmolarity and osmotic diuresis with significant fluid and electrolyte losses, often exacerbated by vomiting.

The dual aims of treatment are to restore fluid and electrolyte deficits and to terminate the driving lipolysis and ketogenesis. Insulin is effective therapy, inhibiting gluconeogenesis, lipolysis and ketogenesis, and increasing peripheral glucose utilisation. Current guidelines recommend insulin at 0.1 U/kg/h (with or without a bolus dose) rather than a variable dose based on blood glucose level (BGL), because insulin resistance is more common as bodyweight increases.<sup>7,8</sup> Historically, higher insulin doses were used but hypoglycaemia was frequent.<sup>9</sup> The guideline targets for reduction in BGL (based on expert opinion) are typically 3–4 mmol/L/h until BGL reaches 10–15 mmol/L. Then intravenous glucose should be added and insulin continued (often at a reduced rate) until ketoacidosis resolves, as determined by 3-beta-hydroxybutyrate levels. These recommendations are derived from the higher risk of hypoglycaemia with more aggressive glucose reduction, and the association between a rapid fall in osmolarity and the development of cerebral oedema, especially in children, although other factors may also contribute to this complication.

In this issue of the Journal, Mårtensson and colleagues describe the differences in the incidence of hypoglycaemia, hypokalaemia and hypo-osmolarity and in hospital mortality in two cohorts of patients distinguished by early BGLs in the intensive care unit. From the Australian and New Zealand Intensive Care Society Adult Patient Database (APD), 8553 patients assigned an ICU admission diagnosis of DKA between 2000 and 2013 were identified. The database included the highest and lowest recorded values of several biochemical measurements in the first 24 hours of ICU

admission; patients with neither BGL measurement greater than 10 mmol/L were considered to have received intensive early correction, and the remainder were considered to have received partial early correction.

Patients in the intensive correction group were found to have hypoglycaemia (at least one of the two glucose values < 4 mmol/L) and hypo-osmolality (< 285 mmol/L, calculated from non-synchronous values) significantly more frequently than patients in the partial early correction group. Hypokalaemia (< 3.3 mmol/L) and hospital mortality (1.8% v 1.4%;  $P = 0.42$ ) did not differ between the groups. However, when adjusted for severity of illness using a propensity score based on the Australian and New Zealand Risk of Death (ANZROD) model, excluding glucose values, the odds of hospital mortality were significantly lower in the partial early correction group (odds ratio, 0.44; 95% CI, 0.22–0.86;  $P = 0.02$ ). Further, when stratified by highest glucose level, the adjusted odds of hospital mortality were lowest in patients with moderate BGL correction (10–20 mmol/L).

As well as the usual limitations of observational studies noted by the authors, the ANZROD model has not been validated in DKA, and may not be appropriate for the unusual clinical and biochemical features of DKA. This study could also be criticised for the lack of confirmation of the diagnosis of DKA, the lack of pre-ICU glucose values, the use of biochemical measurements from unknown times during the first 24 hours in the ICU, and the use of the same glucose values for group assignment and the determination of hypoglycaemia. However, in the absence of randomised clinical trials, the study provides support for the current guidelines to avoid aggressive correction of hyperglycaemia and suggests that moderate correction may be the “sweet spot”.<sup>10</sup> Moreover, as new approaches to the treatment of diabetes develop,<sup>11</sup> as we understand more about the impact of prior hyperglycaemia on glucose targets<sup>12</sup> and as we develop new technologies to monitor BGLs in the ICU,<sup>13,14</sup> such pursuit of the “sweet spot” will become more refined.

This study illustrates that, as we have found more potential for harm from our treatments, we may now be at the point in intensive care where the quest has become not to discover how close to normal it is safe to go but, rather, what level of abnormality will still allow recovery?

### Competing interests

None declared.

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