Diabetic ketoacidosis 1950 onwards

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Today's diabetes world is fast-moving and exciting; knowledge is accumulating at an astonishing rate. To help understand the present, however, it sometimes helps to examine the past.

In this installment of *Tattersall's Tales*, Robert Tattersall explores the history behind our understanding of the acute complications of diabetic ketoacidosis, looking back at key developments with regard to its presentation, diagnosis, treatment and prevention.

From 1950 to 1975 diabetic ketoacidosis (DKA) continued to be a common, and frequently fatal, medical emergency. Lists of precipitating factors were compiled retrospectively and were usually guesstimates rather than hard facts. In virtually all series, the commonest cause was "infection" although this was probably an overestimate since it was all too easy to make vomiting and a leucocytosis add up to "gastroenteritis" or "urinary tract infection". Deliberate omission of insulin was strikingly absent. In all series a fifth of cases occurred in those with previously undiagnosed diabetes and in another quarter or more the cause was unknown. These lists were compiled by doctors and there was, as in the 1930s, a tendency to blame the patient. However, during this period diabetes services were generally poorly organised and it was difficult for patients to get emergency advice. In the United Kingdom, they could only get this "out of hours" either from their GP or by going to the accident and emergency department. Furthermore, general practitioners did not necessarily give good advice because they had been deskilled by the assumption that type 1 diabetes and its management was the preserve of hospitals (Bingle et al, 1971).

Once the patient reached hospital, he or she was treated by the firm on take without the benefit of any protocols. There were many unresolved issues.

One was how much insulin? In the late 1930s doses tended to rise and starting with 100 units became the norm. High-dose regimens became established after the war as a result of two authoritative reports, one from the USA and one from Britain. Howard Root's 1945 paper from Joslin's unit compared 478 cases treated between January 1923 and August 1940 in which the mortality was 12% and 123 cases between 1940 and May 1944 with only two deaths (1.6%). Analysis of their last 123 cases had, according to Root, shown a clear relationship between insulin dose and the level of blood sugar so that patients with an initial level of 72–89 mmol/L "needed" an average of 1224 units in the first 24 hours. He recommended that the most seriously ill should be given an initial dose of 100 units subcutaneously and 50 units intravenously with a second dose half an hour later (Root, 1945). A paper with the same message was published in England in 1949 from the Birmingham diabetic clinic recommending 200–400 units at once intravenously, then 50 units every 30 minutes until the urine was free of acetone (Black and Malins, 1949).

When I qualified in 1968 it was rare for one treatment regimen to be recommended by more than one "authority". As one paper put it: "The treatment of DKA is clouded by a confusion of insulin dosages and administration routes" (Kidson et al, 1974). One thing that was generally agreed was that insulin should be given intravenously in the shocked and dehydrated patient; what was not understood until the early 1970s was that its half life, when given intravenously was only 3–5 minutes. In 1972 Peter Sönksen showed that continuous infusion at only 2–12 units/hour was effective in regulating blood glucose concentrations (Sönksen et al, 1972). Many believed that this was not relevant to DKA, which was thought to be a state of insulin resistance. However, in 1974 a study of 38 patients with DKA from four English centres showed that continuous low-dose intravenous infusion of insulin at an average dose of 7.2 units/hour was simple, safe and effective (Page et al, 1974). Advantages suggested for this regimen were lower risks of hypokalaemia and hypoglycaemia and the nebulous concept that it was "more physiological" and produced a smoother metabolic recovery.

Where facilities were less sophisticated another low-dose regimen was that of intermittent intramuscular injections of 10 units hourly, the so-called Alberti regimen (Alberti et al, 1973). Few realised that a low-dose regimen had been used with great success in Karlsburg, East Germany from 1946 (Menzel et al, 1976) and the work of Sönksen, Alberti and others was regarded with great suspicion, especially in the USA. In an editorial in the *New England Journal of Medicine* in 1976, Leonard Madison summarised the concerns of many Americans:

> "*There is no doubt that many patients with diabetic ketoacidosis will respond to low-dose continuous insulin infusion. It is more pertinent, however, to ask how many will not respond. Put in another way, how many lives will be lost as a consequence of inadequate insulin administration because of the present unwarranted enthusiasm for and use of progressively decreasing amounts of insulin in the treatment of diabetic ketoacidosis?" (Madison, 1976)*

Whether bicarbonate (HCO_3) should be used in the treatment of DKA has been a subject of contention for more than 70 years. In the 1930s Joslin was vehemently opposed to its use whereas Alexis Hartmann (of the eponymous solution) was enthusiastically in favour. This dichotomy continued into the 1980s with proponents of HCO_3 claiming that acidosis should be reversed as quickly as possible since it impaired cardiac contractility and caused vasodilation. Opponents claimed that HCO_3 increased the risk of hypokalaemia, caused paradoxical cerebrospinal fluid acidosis and tissue hypoxia and might be one cause of the devastating complication of cerebral oedema. The few randomised trials which have been done have

been small and inconclusive and it seems unlikely that a definitive trial will ever be done. Thus we are left with the situation where most diabetes physicians advise against HCO_3 while intensivists swear by it.

In the past 30 years there has been considerable improvement in the outcome of DKA in the UK and other Western countries. A Danish study covering the period 1996 to 2002 found that, nationwide, there were 4807 admissions and 137 deaths. As in all studies, mortality was substantially higher in older patients; in those over 70 years old mortality was seven-fold higher than in younger patients (15% vs 2%). In 77% of deaths there was a cause other than pure DKA, usually heart disease or infection (Henriksen et al, 2007).

In Birmingham, UK, between 2000 and 2009, 137 patients (28 with previously unknown diabetes) had 278 episodes of DKA. Overall, five died (1.8%), all of whom had significant comorbidity contributing to death: pneumonia (two cases), gastrointestinal bleeding, alcoholic liver disease, and chronic renal failure (Wright et al, 2009).

What remains troubling is that the incidence of DKA has not declined over the past 30 years, nor has the proportion of young patients with new type 1 diabetes who present with DKA – around a quarter. In many of these cases, the GP has been consulted several times but failed to recognise obvious signs of diabetes. In a recent case a 20-year-old shop assistant had been in bed for 5 days with a diagnosis of "vestibuloneuritis"; the GP was concerned that the continued vomiting could be causing dehydration so asked about her urine output . Her mother answered that she was passing "a huge amount of urine and was drinking a lot". The GP recorded: "Good urine output, drinking well, not dehydrated. Continue treatment." Two days later, when she was unrousable, her mother dialled 999. The patient was left with serious neurological impairment and the case was settled by the Medical Protection Society for a large sum (Medical Protection Society, 2011).

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