Title

Recurrent diabetic ketoacidosis and a brief history of brittle diabetes research: contemporary and past evidence in diabetic ketoacidosis research including mortality, mental health and prevention

Running title

Contemporary and past evidence in recurrent diabetic ketoacidosis

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Conflicts of interest

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Novelty statement

- Diabetic ketoacidosis (DKA) continues to be a common cause of admission in Type 1 diabetes and is the leading cause of mortality in young people with Type 1 diabetes. DKA suggests all-cause mortality over 15% at 5-year follow-up.
- This review brings together the limited current evidence in DKA prevention and links it with the mental health literature of DKA and the

historical literature of brittle diabetes, a significant component of which comprised people with recurrent DKA.

- From a clinical perspective, more caution is required in assessment and management of people with recurrent DKA given the potential for a treatable mental health condition and substantial risk of early mortality.

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Abstract

Pharmacological, technological and educational approaches have advanced treatment of Type 1 diabetes in the last four decades and yet diabetic ketoacidosis (DKA) continues to be a leading cause of admission in Type 1 diabetes.

This article begins by reviewing the contemporary epidemiological evidence in DKA. It highlights a rise in DKA episodes in the last two decades; that DKA continues to be the leading cause of death in young people with Type 1 diabetes and that DKA episodes are a marker for subsequent all-cause mortality. It also summarises the limited evidence base for DKA prevention and associations with psychopathology.

To emphasise the importance of this group with high-risk Type 1 diabetes and the degree to which they have been overlooked in the past two decades, the

article summarises the research literature of recurrent DKA between 1976-1991 when it was extensively investigated as part of the phenomenon of ‘brittle diabetes’. This period saw numerous basic science studies investigating the pathophysiology of recurrent DKA. Subsequently, research centres published their experiences of ‘brittle diabetes’ research participants manipulating their treatment under research conditions. Unfortunately the driver for this behaviour and whether it was indicative of other people with DKA was not pursued.

In summary we suggest there has been a stasis in the approach to recurrent DKA prevention, which is likely linked to historical cases of mass sabotage of ‘brittle diabetes’ research. Further investigation is required to clarify possible psychological characteristics that increase risk of DKA and thereby targets for DKA prevention.

Introduction

Diabetic ketoacidosis (DKA) is a preventable condition: the leading cause of DKA admission is insulin omission (1). That admissions are associated with high HbA1c suggests a degree of chronicity in underuse of insulin prior to the episode (2). Complete or near complete absence of insulin leads to hyperglycaemia through the failure of insulin-mediated cellular uptake of glucose and fatty acid breakdown becomes unregulated resulting in ketone production and acidosis. If untreated or unrecognized, coma and death occur within 3-4 days.

The acute medical management of DKA episodes has been increasingly refined and standardised. Global institutions such as International Society for Paediatric and Adolescent Diabetologists (ISPAD) and European Association of Diabetes (EASD) have worked towards unified protocols for the treatment of DKA and in UK, Joint British Societies of Diabetes have published guidelines for DKA. Association of British Clinical Diabetologists has documented the increasing uptake of such management pathways (3).

The fall in mortality from DKA over the last few decades is believed to be associated with these organizational changes, as is the decrease in bed stay and admissions to intensive care (4).

However, where DKA treatment has progressed substantially in the last four decades, prevention of DKA episodes has not kept pace: Zhong and colleagues found a 53% increase in DKA episodes over a 15 year period at English hospitals (5), whilst DKA continues to be the leading contributor to

loss-of-life expectancy in years under 50 with Type 1 diabetes (6). Our understanding of the circumstances leading to DKA and evidence from prevention interventions is limited.

This review will highlight the contemporary evidence in DKA alongside historical research in 'brittle diabetes', a clinical description, which in part, featured recurrent DKA. In 1977, Robert Tattersall published a review paper on 'Brittle Diabetes' in which he evaluated the contemporary understanding of the disorder and provided a definition of the syndrome (7):

'For the purposes of the practising physician, the brittle diabetic is most simply defined as the patient whose life is constantly being disrupted by episodes of hypo- or hyperglycaemia whatever their cause…'

Although frequently cited in the following decade, this definition and the term 'brittle diabetes' have fallen in use over the last 25 years, with mostly non-English language researchers in islet cell and transplantation research continuing to use the term. The evidence base for causes and management of frequent and severe hypoglycaemia has subsequently developed with proposed guidelines delineating use of education, technology and transplantation (8). However, the second substantial element of 'brittle diabetes' was recurrent diabetic ketoacidosis (rDKA) and it is our contention that this is a neglected area of clinical research and worthy of re-evaluation. Therefore alongside a review of current epidemiology, associated mortality, prevention and links with mental health presentations, we also summarise the research literature of rDKA during the late 1970s to early 1990s when it was extensively investigated as part of the phenomenon of 'brittle diabetes'. During this period several research centres investigated the pathophysiology

of ‘brittle diabetes’ and used early prototypes of continuous subcutaneous insulin infusion (CSII) and artificial pancreas to prevent admissions. However, results were disappointing and unfortunately the possibility of a psychiatric condition that emerged during these studies was not investigated in any detail, with the difficult experiences of researchers only acknowledged many years later (9). Though this period ended without a breakthrough, the number of centres and attempts at intervention indicate the seriousness of the collective undertaking and emphasise the need for further endeavour in this area of Type 1 diabetes research.

Epidemiology of DKA

Incidence of DKA varies across different countries, with a recent systematic review in adult Type 1 diabetes populations indicating a range between 8-56 episodes per 1000 person years (10). Studies investigating rate of change of DKA frequency within a population in the last two decades vary in methodology, whether they discern between Type 1 and Type 2 diabetes, how they account for underlying changes in diabetes populations and definition of DKA per se (5,11,12). However, the two most recent of these studies indicate increases in DKA episodes in different parts of UK, Wales and England, the latter of which indicates an incident rate ratio of 1.53 over 15 years between 1998-2013 after adjustment for increases in the Type 1 diabetes population. Across child and adolescent and adult populations, studies indicate that DKA episodes are associated with high HbA1c, lower socioeconomic groups and non-white ethnicity and whilst there is equal

preponderance of females and males for single episodes of DKA, rDKA is associated with increased frequency in young women (10,13).

Mortality at DKA episode and at follow-up

Mortality for an inpatient DKA episode in a developed world healthcare service is less than 1% (4,14). However, all cause mortality at follow-up after DKA episode(s) ranges between 13-17% implying that DKA is a marker for underlying mortality risk (2,14,15). A national retrospective longitudinal study based in Taiwan published in 2016 followed people after a DKA episode for up to 8 years after admission and indicated all-cause mortality of 17.7%, with a hazard ratio four times greater than the background population after adjustment for age and gender (15). These figures are supported by further retrospective longitudinal studies from the same year. For example, Gibb and colleagues assessed mortality at a large single centre in Edinburgh over 6 years and found mortality of 14.8% (14). It should also be noted that mortality risk across both studies increased in those individuals having recurrent episodes, with mortality of 29.6% in those people with 4 or more episodes in the Edinburgh study. It should also be noted that 19 of 44 deaths (43.2%) in the Edinburgh study were of uncertain cause, with median age of 31 years.

Health service use and cost in DKA

Evidence for health service costs of DKA and rDKA populations is very limited and where studies are available data are not immediately comparable due to differences between private and publicly funded healthcare systems.

However, studies demonstrate that private healthcare systems appear to result in greater numbers of DKA admissions in people with limited or no health insurance, the urban ethnic minority communities in US being particularly vulnerable in this regard (2). In addition, costs accrued for hospital activity per se is recognised as markedly different between US and other healthcare systems. For example, in the same year, Shresthra and colleagues in US and Icks and colleagues in Germany conducted cost analyses of child and adolescent populations with Type 1 diabetes, with and without DKA episodes (16,17). In US, there was a 42% increase in mean cost from no DKA episode to one DKA episode in a calendar year, whilst in Germany there was over a 100% increase in mean costs. Although this might initially suggest costs in Germany to be greater, much of this difference is accounted for by greater baseline costs for US outpatients with Type 1 diabetes. Icks and colleagues also note the marked difference in DKA frequency between the two populations, with US population having over three times as many DKA episodes. In the UK, Dhatariya and colleagues performed a detailed ground level cost analysis of adult DKA treatment using a national survey as their benchmark. They included clinician time, diagnostic tests and intravenous medication in their calculations, reporting a mean price of £2064 per DKA admission, though their mean bed stay was longer than other published studies in this area. This cost is over double the current UK Best Practice Tariff (18,19).

DKA and mental health

Given the association of raised HbA1c in diabetes distress, depression and anxiety (20), it is perhaps unsurprising that DKA presentations are associated with mental health problems. Though studies are limited in number there has been consistent evidence over 60 years for associations between DKA and psychiatric diagnoses, personality characteristics and family and relational difficulties and often suggesting a premorbid pattern of emotional difficulties in individuals or their family members prior to diagnosis of Type 1 diabetes. For example, Bryden and colleagues comprehensively assessed the physical and mental health of adolescents with Type 1 diabetes with follow-up in early adulthood and whilst diagnosis at baseline of a psychiatric condition predicted future DKA episodes, DKA at baseline predicted future diagnosis of a psychiatric condition at 10-year follow-up (21).

However, in the modern literature of the last 15 years there has been very limited research into the mental health of DKA and rDKA populations, and even fewer studies using direct psychological or psychiatric assessment. One rare example is a large single centre study, in which Randall and colleagues compared individuals with single DKA episodes with rDKA (22). Although history of depression, higher rates of alcohol misuse and homelessness were more frequent in rDKA, there was no difference in depression scale or quality of life measure. However, this study has several marked limitations including lack of a non-DKA control group and a lack of comprehensive psychological assessment, with use of only two limited psychological tools (22). An alternative, though less precise measure of association with DKA is use of proxy markers for psychiatric conditions in health databases. Schulman and colleagues used a large multi-centre health database to suggest an

association in frequency of DKA episodes with mental health appointments, which was potentiated by lower socioeconomic status (23).

DKA prevention interventions

There are limited examples of studies attempting to prevent DKA episodes and very few have used a psychological therapy as the fulcrum of the intervention. Ellis and colleagues conducted a randomised controlled trial of a 6 month home-based family therapy intervention for adolescents with high-risk Type 1 diabetes, which showed a sustained decrease in DKA episodes and HbA1c after 24 months with a cost saving despite the relatively intense and resource heavy intervention (24).

Other studies aimed in part or wholly at DKA reduction have focussed efforts on maintaining continuity with at risk populations and providing a coherent multi-disciplinary service including 24-hour emergency phone advice. Farrell, Holmes-Walker and colleagues have published two papers detailing the impact on DKA admission and glycaemic control of a specialist transition diabetes service between paediatric and adult services, focussed on maintaining a therapeutic relationship during a period of the person's life when circumstances are in a state of flux including entering higher education, finding work and establishing a family life (25). Although there are no control groups to establish how participants might have fared without intervention across the 2 studies, the substantial and sustained fall in single DKA and rDKA episodes after 10 year follow-up suggests an impact on behaviour at time of DKA crisis. However, mean HbA1c remained unchanged, suggesting

long-term behaviours regarding diabetes self-management were not affected. In addition, despite the prolonged follow-up the authors do not make reference to mortality in the cohort. Similarly, Ilkowitz and colleagues and Simmons and colleagues have published findings in paediatric and adult diabetes services respectively, using a comprehensive multidisciplinary approach to managing people with DKA, with a positive impact on admission rate (26,27). Both services emphasise a need for additional support in this at risk group and a coherent method of tackling an individual's difficulties in managing diabetes, which included individual diabetes education and use of insulin pump technology where appropriate. However, the lack of a control group in both studies and the use of several treatment approaches make it difficult to draw conclusions regarding efficacy and which elements might be beneficial.

rDKA in brittle diabetes research: 1976-1991

From the late 1970s to mid-1980s, groups of people with rDKA, were extensively investigated in several international clinical academic units. In UK, two centres established themselves as centres of excellence in this area: Newcastle University and Guy's Hospital Medical School, London. Perhaps because of the dearth of modern studies on rDKA, this research continues to be referenced by contemporary authors (14).

Starting in 1976, the Guy's team successfully trialled CSII and within several years were deliberating its use in the outpatient setting (28). This success led to many referrals from clinicians struggling to manage, 'brittle diabetics' with

‘frequent, unpredictable episodes of ketoacidosis’. **Although subsequent trials** of CSII in this group **were not successful,** metabolic control was achieved with continuous intramuscular insulin infusion and therefore ‘brittleness’ was **theorised to arise from subcutaneous pathophysiology, such as** impaired blood flow or enzymatic action (29). In the years following 1980, the unit at Guy’s undertook numerous studies to investigate these theories (30).

During the same period the Newcastle University Metabolic Unit **also became recognised as a specialist centre with innovations including a** glucose controlled insulin infusion system (GCIIS; artificial pancreas) **leading to referrals** of people with rDKA (31). Studies at Newcastle compared metabolite and hormone levels in **people with or without brittle diabetes** (32), whilst a further experiment was conducted on the action of insulin on adipocytes comparing insulin binding and degradation (33).

These institutions were not unique. Over the same period other UK and international academic centres published similar investigations. David Henry et al at City Hospital, Nottingham, detailed an experiment indicating delayed subcutaneous absorption of radiolabelled insulin and describe what would become the classical ‘brittle diabetes’ research participant: ‘an 18 year old [female] nursing student’ with varying, sometimes with ‘very high’, insulin requirements (34).

In 1978 a New Zealand research group published an article detailing a number of studies involving a young woman with severe insulin resistance and suggested rapid insulin degradation **as a** mechanism of resistance **and trialled aprotinin (a protease inhibitor) to prevent insulin breakdown** (35).

A year later Friedenberg et al, in USA, published what they deemed to be a successful trial of subcutaneous aprotinin, **in 5 young women participants** though response to treatment appears mixed and not sustained (36). Guy's Hospital also trialled apropotin as treatment **for rDKA** with mixed results and they subsequently proposed a theory that the aprotinin diluent was acting as a vasodilator. This led to further trials at Guy's using electronic plethysmography, demonstrating that it was likely that rather than preventing insulin breakdown, the aprotinin was causing a vasodilatory effect leading to increased insulin uptake (37).

With clinicians struggling to stabilise people with recurrent and lengthy DKA admissions there was an imperative to find workable outpatient solutions, leading to different technical innovations. In 1979, Diaz-Pereda in Cincinnati, USA, described use of an arteriovenous shunt and intravenous insulin in a young man with rDKA and 'insulin resistance who seemed to metabolize insulin at the injection site' (38). Perhaps heralding later observations by other researchers, Diaz-Pereda noted certain behaviours in this person that worked against clinical improvement including irregular consumption of 'concentrated sugar or soft drinks', 'lapses of memory in regards to refilling the syringe, recharging the batteries and changing the rates of delivery'. In 1982, Schade and colleagues in Albuquerque, USA, published a paper describing their experiences of 3 young people with 'brittle diabetes' with failed intramuscular and intravenous access and go on to describe their development and trial of a subcutaneous peritoneal access device deeming it a success with no complications after 9 months follow-up (39). However, other sites had less

success with this method of insulin delivery and a member of the Newcastle cohort died during insertion of a peritoneal catheter (40).

After the numerous biological studies investigating brittle diabetes during this period, a small number of publications described extensive sabotage of investigation procedures by a significant number of research participants. The first was an account from the Newcastle group published as an abstract at the EASD meeting in September 1984 (41). Detailing factitious instability in over 50% of their cohort of 19 research participants, they also relate the experience of ‘a serenity and optimism at odds with their predicament’ in 14 participants, a psychological archetype also noted at Guy’s and later described by Gareth William’s as a ‘Mona Lisa-like smile’ (9). The Newcastle group also described a variety of methods of manipulation including ‘stopping injections’, ‘massive overeating’, ‘dilution of insulin with tap water’, and ‘factitious hypoglycaemia’. A review paper on ‘brittle diabetes’ the following year by the same authors presents biological and psychological aetiologies, illustrated with case histories, including a young woman, again employed as a nurse, not appropriately responding to her hyperglycaemia and a young woman with unusual bacteraemia found to have diluted her insulin with tap water (42). Except for the superficial observation that hospital was preferred to home in a number of this group, their psychological formulation is very limited. **Earlier the same year, the Albuquerque group published a case series of 30 people with ‘brittle diabetes’ with similar experiences of self-destructive behaviours including self-induced hypoglycaemic seizure, injection of heparin to induce bleeding and sabotage of infusion sets to induce ketoacidosis** (43)**.**

Later in 1985, Greg Wilkinson, a psychiatrist at Institute of Psychiatry and involved in assessing the Guy's cohort, published the only standardized psychometric assessments of a 'brittle diabetes' cohort during this period (44). In a letter written to the British Medical Journal, he briefly details assessment of 7 research participants using a standardized psychiatric assessment as well as personality and eating disorder questionnaire. All 7 were deemed psychiatric cases, but 'did not have well defined psychiatric conditions'.

Robert Tattersall's frequently referenced 'brittle diabetes' definition from 1977 is from an article extensively reviewing the biological and psychological literature in this area. Tattersall astutely states 'Those who have not developed a mature response to stress or frustration may attempt to resolve all conflicts in terms of diabetes'. Somewhat presciently he also states that 'emotional problems in brittle diabetes are often recognized late, usually after years of fruitless attempts at regulation'. In a BMJ editorial eight years later, Tattersall reflects again on the 'brittle diabetes' definition and the research of the intervening period and points to the difficulties that diabetologists have with this group of patients (45). Having earlier referred to his colleagues as 'happy to off load' these patients to tertiary services and pointing out difficulties inherent in managing a patient 'branded as a liar', he observes a 'great fear' in his colleagues of 'missing organic disease'. For the tertiary centre managing such off loaded patients the experience appears equally bleak. Harry Keen in the closing paragraphs of his introduction to 'Brittle Diabetes' describes clinicians at 'the end of the road' with 'an unexplained problem and a set of unverifiable suspicions' and 'in a state of defeat and

despair, parents and friends in anxiety and disappointment but the patient placid, somehow defiant and even, dare one say it, triumphant' (46).

It is perhaps unsurprising that following such negative experiences the study of this group of people reduced with numbers of publications on 'brittle diabetes' decreasing markedly in the following years. However, in 1991, as a coda to this period, Tattersall et al published a 12 year follow-up of 30 people with 'brittle diabetes' whilst Gill and Alberti published follow-up of 20 patients from their Newcastle cohort (40,47). Both studies indicate marked falls in DKA episodes but sustained high HbA1c and mortality at 10%.

It remains curious that the mental health line of inquiry was not pursued as a potential method of managing people with rDKA, though it should be noted that none of these studies has psychiatrists in their group. However, a recent review of Munchhausen's syndrome reviewing 455 published cases over a 50-year period has striking parallels (48). Their group are also majority young women, often with a healthcare background and self-induced illness and they also include within their cases a group of people with either self-induced hypoglycaemia or DKA. It is likely, therefore, that these historical cases with 'brittle diabetes' were part of this diagnostic group and it is interesting to note that the Munchausen cohort often have depression and personality disorder as part of the underlying psychiatric presentation, both of which are amenable to psychiatric intervention.

Conclusion

DKA prevention has not advanced in the last two decades despite the improvements in pharmacological, technological and educational approaches to Type 1 diabetes and this group remain a vulnerable, high-risk group. This review summarises what was learnt during a period when greater research attention was given to the rDKA group and emphasises that psychopathology was a primary cause.

From a clinical perspective, a broad approach is necessary in assessment and management of people previously referred to as ‘brittle diabetics’ where lives are disrupted with multiple admissions. In severe hypoglycaemia a proposed guideline is already in place, which delineates the technological, educational and psychological approaches (8). Similarly, for the person presenting with rDKA an acknowledgement of potential physiological causes as well as psychological and educational aspects of insulin delivery should be considered. This should start with a thorough clinical history and examination as well as assessment of insulin injection technique. In our experience, most patients admit to insulin underuse and acknowledge the role of their mental health in struggling with Type 1 diabetes self-management. In this situation, liaison psychiatric assessment as an inpatient prior to discharge is beneficial to highlight acute psychiatric risk related to self-harm and suicidality. This element of assessment will also guide as to requirement for psychopharmacological treatment and signpost for the most appropriate psychological support in primary or secondary care. Where a mental health or injection technique issue is not apparent, we recommend screening for physiological causes of DKA such as occult infection. Screening for subcutaneous insulin resistance is only deemed necessary if glucose control

is achievable under intravenous insulin, but lost when converting to subcutaneous insulin. When assessing for subcutaneous insulin resistance we emphasise to the patient that we are open minded to the cause of their rDKA and that assessing for insulin resistance under controlled conditions is the optimum method of assessment and removes any doubt as to whether insulin is being correctly injected.

In addition, we also recommend for individual hospitals to develop systems for database surveillance in order to highlight which patients are having recurrent admissions. This will enable clinical services to adapt clinical management to this high-risk group and aid clinical governance in this area.

From a research perspective, clarification of possible psychological characteristics that might increase the risk of DKA/rDKA is necessary to focus the design of a psychological intervention for DKA prevention and potentially reduce risk of early mortality. In addition, understanding the health service use and costs of this group (outside of DKA per se), will help calibrate the intensity of such an intervention and thereby increase the likeliness for it to be taken on in clinical practice. It is also notable that if static psychological factors (eg. traits associated with personality) are relevant in DKA/rDKA, it is possible that mental health screening at T1 diagnosis could indicate future high-risk in DKA and early mortality.

Beyond this, the notable loss of rDKA research after the period of intense interest in the 1980s is curious, particularly when contrasted to severe hypoglycaemia, the other component of ‘brittle diabetes’. The loss of academic interest in this area is not immediately explainable, but could be

linked to the negative experience for researchers repeatedly exposed to factious behaviour in **a sub-group of people with rDKA**.

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