Full title: The psychopathology of recurrent diabetic ketoacidosis: a case-control study

Short title: Psychopathology of recurrent diabetic ketoacidosis

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Novelty statement

- This is the first case-control study to investigate psychological factors associated with recurrent diabetic ketoacidosis.

- We find that recurrent diabetic ketoacidosis is associated with elevated anxiety, diabetes distress, emotion regulation difficulty and personality dysfunction.

- Mental health assessment at time of diabetic ketoacidosis with subsequent follow-up could reduce potential admissions.

Abstract

Background

Despite its poor prognosis, the psychological factors associated with recurrent diabetic ketoacidosis are poorly understood. In people with type 1 diabetes, we assessed for psychopathology in those with and without recurrent DKA.

Method

The design was a case-control study. Cases were defined as people with two or more DKA episodes in a 12-month period (recurrent DKA). Cases and controls were matched for gender and age. We compared groups for scores on Beck's Anxiety Inventory (BAI), Beck's Depression Inventory II (BDI-II), Difficulty in Emotion Regulation Scale (DERS), Experiences in Close Relationships-Revised (ECR-R), Standardised Assessment of Personality-Abbreviated Scale (SAPAS), Interpersonal Problem Inventory (IIP-32), Eating Disorder Examination Questionnaire (EDE-Q) and Problem Areas in Diabetes

(PAID) using unpaired t-tests or Mann-Whitney U tests for parametric- and non-parametric data respectively. Correction was made for multiple testing.

Results

Twenty-three cases and 23 controls were recruited with mean age 31.0 (11.4) years and 65.2% were men. Cases had higher HbA1c levels than controls (101.1 (23.2) vs 85.7 (21.7) mmol/mol, p=0.02. Compared to controls, people with recurrent DKA had higher scores on the BAI (p=0.004), PAID (p=0.004), DERS (p=0.001) and SAPAS (p<0.001). Sixteen of 23 (69.6%) cases screened positive for a personality disorder compared to 6 of 23 (26.1%) controls.

Conclusions

People with recurrent DKA have elevated levels of anxiety and diabetes distress, greater difficulty with emotion regulation and personality dysfunction compared to matched controls.

Introduction

Diabetic ketoacidosis (DKA) is a principal acute complication of type 1 diabetes. If untreated, DKA leads to death within 3-4 days and is the leading cause of mortality in people with Type 1 diabetes under 30 (1). Despite developments in diabetes education and technology, inpatient episodes of adult DKA have increased consistently over the last 20 years in England and the USA (2) (3).

National and international associations of diabetes clinicians and researchers have repeatedly asserted the importance of DKA prevention (4), though there is limited evidence of how this can be achieved (5).

Database studies have indicated an association between psychiatric diagnoses or contact with mental health services and DKA episodes. In a population-based cohort study, Shulman and colleagues found an association between psychiatric appointments in people with Type 1 diabetes and subsequent DKA admissions (6). One study has performed psychosocial assessment of people with DKA. In that cross-sectional study comparing individuals with a single DKA versus recurrent DKA there was no difference in their assessment (7). However, as well as lacking a non-DKA control group, the psychological questionnaires were conducted at the time of DKA admission and limited to a brief depression scale and quality of life questionnaire. A case-control study conducted psychiatric assessments on people described as having 'brittle diabetes', a study population having frequent admissions with Type 1 diabetes (8). However, the study did not quantify numbers of people with recurrent DKA only describing them as having 'glycaemic instability'. Therefore their finding of an association

between 'brittle diabetes' and cluster B personality disorder is difficult to interpret.

Clarification of whether specific psychiatric or psychological difficulties are associated with DKA could move services closer to using mental health treatment as part of the management of recurrent DKA. Although DKA remains relatively understudied, several psychological variables are known to be associated with high HbA1c, which is itself associated with higher frequency of DKA (9). Depressive and anxiety symptoms have been associated with hyperglycaemia in Type 1 diabetes, mediated through sub-optimal diabetes self-management (10,11). In a meta-analysis, eating disorder symptoms were associated with hyperglycaemia in Type 1 diabetes (12). Alexithymia, a difficulty with recognising and regulating emotions, has been found to be associated with higher HbA1c (13). In addition, diabetes distress, which has an established body of evidence linking higher levels with higher HbA1c, has also been suggested to be linked to difficulties with regulating emotion (14).

Attachment theory proposes that early experiences of care giving predict later ability in social functioning and emotion regulation. Ciechanowski and colleagues investigated the significance of adult attachment relationships on glycaemic control and health outcomes in multiple studies in people with both Types 1 and 2 diabetes, finding associations between hyperglcaemia and insecure attachment as well as greater frequency of complication and mortality (15). Their central hypothesis was that people less able to sustain relationships find it harder to maintain therapeutic relationships with health services. This might also be a factor in people having recurrent DKA. Finally,

personality disorder is under-recognised and a core aspect is the enduring nature of symptoms (16). Therefore early recognition could be potentially beneficial to long-term management within a diabetes service.

We aimed to describe and compare differences in mental health symptoms and psychological functioning between people presenting with recurrent DKA and without recurrent DKA.

Compared to controls, we hypothesized that people with recurrent DKA would have higher levels of diabetes distress, depression, emotion regulation difficulty, adult attachment insecurity, interpersonal difficulty and eating disorder symptoms.

Methods

Design and setting

This is a case-control study comparing people with recurrent DKA with non-recurrent DKA controls. Participants were recruited from four hospitals in two geographical areas, south-east London (King's College Hospital, University Hospital Lewisham) and south-west England (Southmead Hospital and Royal United Bath). Ethical approval was granted by the North East (York) Research Ethics Committee (16/NE/0223). Recruitment took place between December 2016 and February 2017. All participants gave written informed consent.

Recruitment

A list of all DKA episodes in the preceding three years was generated at each site from hospital electronic records. Medical records were then assessed for

inclusion and exclusion criteria and whether DKA criteria were reached for admissions (urine ≥3+ ketones and arterial blood gas pH < 7.35).

All potential participants received a letter requesting their participation in the study and asking them to contact the research team for an appointment. If they did not respond, they were contacted by telephone. After recruitment of an eligible case, potential control participants were identified from a list of people with Type 1 diabetes generated by the local service who had not had two or more DKA episodes within 12 months, lived in the same borough and matched for gender and age (±5 years). Controls were contacted using the same method as cases and underwent the same assessment. If a control did not make contact with the research team, the next person on the list was contacted.

Inclusion criteria for cases were: age 18 years and over; Type 1 diabetes for over two years; two or more diabetic ketoacidosis in a 12-month period within the last three years.

We excluded people with a prior diagnosis of psychotic illness or severe intellectual disability (IQ<35).

Procedure

Assessments were conducted with the support of a research investigator in a diabetes outpatient setting or at the person's home at their request and lasted approximately 1.5 hours. Participants were paid for travel expenses. The participant's glucose meter was downloaded and most recent HbA1c within the past 3 months was extracted from electronic records, and if not available, this was collected after consent.

Psychological assessment consisted of filling online questionnaires via a mental health database (pod-base.org, which is owned by Anna Freud Centre, a large UK mental health research charity) accessed via a tablet computer. Each questionnaire was listed from a homepage and could only be completed once all questions were answered. All participants were offered assistance from the research investigator, by reading stem questions and potential answers. Risk issues were raised in the meeting or following review of questionnaires. These assessments were run in parallel to established diabetes and mental health clinics at King's and Bath where follow-up was available if deemed necessary and was communicated to the general practitioner by letter. Supervision of requirement for mental health follow-up across sites was by CG who was a psychiatry trainee at the time of assessments and conducted all assessments at London sites.

Eight standardized self-report questionnaires were used:

1. Experiences in Close Relationships (ECR-R): 36-item adult attachment assessment tool, assessing two subgroups, attachment avoidance and assessing attachment anxiety. The questionnaire uses a 7-point scale ranging from 1 = strongly disagree to 7 = strongly agree with an average score calculated for each of the sub-groups ranging from 1–7 (17).

2. Beck Depression Inventory – version 2 (BDI-II): standardised assessment tool for depressive symptoms consisting of 21 questions. (18) Each item is scored on a 4-point scale (0–3) with total scores ranging from 0–63.

3. Beck Anxiety Inventory (BAI): standardised assessment tool for anxiety symptoms consisting of 21 questions (19). Each item is scored on a 4-point scale (0–3) with total scores ranging from 0–63.

4. Inventory of Interpersonal Problems (IIP-32): standardised assessment tool for interpersonal functioning consisting of 32 questions including eight subscales (20). Each item is scored on a 5-point scale (0–4) and each subscale scored individually then summed as a total score.

5. Difficulties in Emotion Regulation (DERS) scale: standardised 36-item assessment tool with six subscales regarding emotions (21). Each item is scored on a 5=point scale (1–5) and each subscale is scored individually then summed to make a total score ranging from 36–180.

6. Problem Areas in Diabetes (PAID) scale - a standardised 20-item questionnaire assessing emotion related to the condition including 4 subscales. The questionnaire uses a 5-point scale, the sum of which is subsequently multiplied by 1.25 to make a total score of 0-100 (22);

7. Eating Disorder Examination Questionnaire (EDE-Q) – a standardised 28-item questionnaire measuring degree of eating disorder psychopathology, consisting of a global score as well as 4 subscales (shape concern, eating concern, weight concern, restraint) (23). Each item is scored on a 7-point scale (0–6) and presented as an average for each subscale and an average global score.

8. Standardised Assessment of Personality – Abbreviated Scale (SAPAS) - a standardised 8-item brief screening tool for personality disorder

(24). Each item is scored on a 2-point scale, with no = 0 and yes = 1

(reverse scored for question 3) and presented as a total score.

Sociodemographic factors were also recorded at the appointment by the research investigator including employment (employed/retired/full-time education versus currently unemployed) and relationship status (married or in a relationship versus not in a relationship). Verbal intelligence was estimated using the National Adult Reading Test score - transformed into an IQ score (25) which provides an estimate of premorbid intelligence, in which the average range is 85-115. Biomedical factors were also recorded, including current smoking status, duration of diabetes and prescription of antidepressant medication. We also compared groups for total mean number of glucose tests in prior 28 days as per meter downloads. HbA1c was measured by affinity chromatography (Primus Ultra2, Kansas City, USA) and reported in IFCC (International Federation of Clinical Chemists)-recommended units (mmol/mol) as well as DCCT%.

Statistical analyses

Using IBM SPSS 24.0, the characteristics of the sample were compared between cases and controls. Given the size of the sample, we only used continuous scores rather than binary cut-off scores on the questionnaires, in order to increase statistical power. We also compared the demographic characteristics of recurrent DKA cases who were matched to controls (therefore included in the analysis) against those who were not matched to a control (therefore not included). Data were summarised as mean (SD) or median [interquartile range (IQR)] for normally distributed or skewed data

respectively, or as a count (percentage) for categorical variables. Continuous variables were compared using student's t-test for normally distributed data and Mann-Whitney *U* test for skewed data, and proportions were compared using Fisher's exact test.

Because nine psychological scores were compared (eight questionnaires and ECR-R divided into its sub groups of attachment avoidance and attachment anxiety), we performed Bonferroni's correction for multiple testing by defining a p-value of 0.05/9 (<0.0055) as significant (26).

In clinical studies the SAPAS personality disorder screening tool, has high sensitivity (0.94) and specificity (0.85) at cut-off of 3 (24), but this falls to 0.69 and 0.53 respectively in general populations with cut-off of 4 (27). Though the DKA group is deemed as a 'clinical' population we favoured a more conservative cut-off of 4 in order not to over-estimate the numbers of people with a potential personality disorder.

Sample size calculation: Cohen's d is a standardised measure of the difference between two means, in which values of 0.8 and 1.2 describe large- and very large differences respectively. Using G*Power 3.1 and based on an allocation ratio of 1:1 between cases and controls, we calculated that a sample size of 46 people would be sufficient to large differences (d=0.85) at 80% power and 5% significance on a two-tailed, unpaired t-test. After correction for multiple testing (0.55% significance), this sample size of 46 people would be sufficient to detect very large differences (d=1.15).

Results

A potential 67 people met inclusion criteria and four were subsequently excluded, two having a diagnosis of schizophrenia and two being unable to consent. Thirty-nine of the remaining potential participants were assessed and 23 of these were matched to controls. Compared to the 23 cases matched to controls, the 16 unmatched (not included in the analysis) had a higher proportion of women (75% versus 34.8%, p=0.022, Fisher exact test), but did not differ in age (p=0.19, two-tailed unpaired t-test). Furthermore, the total sample (n=67) had a higher proportion of women than the 23 cases included in the analysis (61.2% versus 34.7%, p=0.03, Fisher exact test). See Figure 1 for full details of recruitment. A total of 23 cases and 23 controls were included in the analysis. The mean age of the sample was 31.0 (11.4) years, of whom 65.2% were men, with average diabetes duration of 14.0 (8.8) years. One of the controls had one DKA during the prior 3 years. Compared to controls, cases were more likely to be unemployed and had statistically lower estimated verbal IQ scores, although both group means fell within the average range of 85-115. No cases or controls had an estimated verbal IQ below 85. Cases and controls had no difference in ethnicity, smoking status, relationship status, duration of diabetes and proportion prescribed antidepressant medication (Table 1).

After correction for multiple testing, cases had higher scores on anxiety, emotional dysregulation and diabetes distress compared to controls, and also scored more highly on the personality disorder measure. There were no statistical differences in depressive symptoms, Experiences in Close Relationships and Eating Disorder scores between the groups, whilst

differences in Interpersonal Problems were not robust to correction for multiple testing (Table 1).

Diagnostic scores: Using a score of four on the SAPAS (personality disorder) scale as the cut-off point, 16 of 23 cases (69.6%) screened positive for a personality disorder in comparison to 6 of 23 controls (26.1%), p=0.0072 for comparison on Fisher exact test.

Discussion

This is the first case-control study assessing the mental health of people with recurrent DKA, a population with high risk for premature morbidity and mortality. After correction for multiple testing, anxiety, diabetes distress emotion regulation difficulty and a personality disorder screening tool were associated with recurrent DKA. Conversely, depressive symptoms, adult attachment relationships and eating disorder symptoms were not significantly different between cases and controls after correction for multiple testing.

. There is growing evidence that emotion regulation is a trans-diagnostic construct, i.e. an underlying mechanism in different types of psychopathology, including personality function, anxiety disorders and substance misuse disorders (28). In addition, personality disorders are frequently comorbid with other mental health disorders such as anxiety disorder (16) and a recent study suggested that a psychological intervention aimed at improving emotion regulation can also improve diabetes distress (14).

Our findings could contribute to an understanding of the poor prognosis of people with recurrent DKA, beyond the risk to health posed by each episode,

particularly if DKA episodes are associated with personality disorder. People with a personality disorder diagnosis have greater physical morbidity with reduced life expectancy by approximately 18 years (16). In addition, anxiety symptoms and diabetes distress predict future glucose control and missed insulin doses respectively (29,30) and this could apply to the recurrent DKA group who at the time of assessment had an average HbA1c of 101.1 mmol/mol (11.4 % DCCT).

Clinical practice emphasizes swift normalization of glucose and ketones with a subsequent brief educational discussion around sick day rules and necessary behaviours to prevent further episodes, with early discharge from acute services (4). Our findings suggest that mental health is potentially a factor in presentation with DKA in some people. Without greater understanding of the psychology associated with a particular admission and diabetes self-management, opportunities to prevent recurrence are potentially missed. For example, did admission occur because the person felt unable to ask for help or was admission related to deliberate cessation of insulin? If the latter, this would represent a form of deliberate self-harm, which in other settings would mandate psychological assessment prior to discharge and a plan for follow-up support. Liaison mental health assessment to clarify the presence of a psychiatric diagnosis and subsequent mental health follow-up could reduce risk of DKA recurrence.

Finally, part of the personality disorder diagnosis is its enduring nature with symptoms presenting during adolescence and continuation into adult life (16). Therefore if future research confirms personality disorder to be an important

factor in recurrent DKA, early recognition could lead to adaptation of the clinical approach and prevent admissions and associated poor outcomes. If not applied universally, screening might be considered after a first non-diagnostic DKA.

The study has some limitations. Its findings are cautioned by the modest sample size, although recurrent DKA is characteristic of a hard-to-reach group. Part of our hypothesis had been that the 'hard to reach' nature was due to avoidant attachment, which was not supported by our study. However, it could be that people who did not attend appointments or were not contactable were exhibiting avoidant attachment. Although self-report questionnaires are likely to correlate partially with one another, correction for multiple testing helped to define the psychological measures most likely to be clinically relevant. The small sample size meant that we were not able to perform multivariate analysis, whilst differences in other measures – notably depression – could become apparent with a larger sample size. Compared to the cases included, those who were unmatched (and therefore excluded) had a higher proportion of women, such that the sex distribution of our cohort is not likely to represent the wider recurrent DKA population. The cross-sectional design means that the directionality of the association between psychological measures and recurrent DKA cannot be inferred, and it is possible that the poor glycaemic control of cases may have itself impacted upon psychological measures. However, it is notable that assessments have been conducted up to 36 months since the first DKA episode and it is unlikely that these DKA presentations per se have led to the psychological differences described. Finally, the National Adult Reading Test was written approximately 30 years

ago, and was updated subsequent to initiation of our study and therefore its use has limitations.

In conclusion, our study indicates a high level of psychological comorbidity in people with type 1 diabetes and recurrent DKA compared to matched controls who do not have recurrent DKA. Longitudinal studies and interventional studies are needed to test whether psychological comorbidity is a modifiable target for the primary- and secondary prevention of recurrent DKA, including its longer-term effects on diabetes complications and mortality.

Competing interests

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Table 1: Comparison of people with recurrent diabetic ketoacidosis with matched controls for sociodemographic factors, biomedical variables and psychological measures

Variable	Category	Total cohort[a]	Cases	Controls	p-value[a]	Number of missing cases
i) Sociodemographic variables						
Age, years (SD)		31.0 (11.4)	30.9 (11.7)	31.1 (11.3)	0.95	0
Sex (%)	Men	30 (65.2)	15 (65.2)	15 (65.2)	-	-
	Women	16 (34.8)	8 (34.8)	8 (34.8)	1.0	0
Ethnicity (%)	White	37 (80.4)	20 (87.0)	17 (73.9)	-	-
	Non-white	9 (19.6)	3 (13.0)	6 (26.1)	0.46	0
Employment status	Employed[b]	33 (71.7)	12 (52.2)	21 (91.3)	-	-
	Unemployed	13 (28.3)	11 (47.8)	2 (8.7)	0.007	0
Relationship status	In relationship	17 (38.6)	6 (28.6)	11 (47.8)	-	-
	Single	27 (61.4)	15 (71.4)	12 (52.2)	0.23	2
Smoker status (%)	Smoker	21 (45.7)	13 (56.5)	8 (34.8)	-	-
	Non-smoker	25 (54.3)	10 (43.5)	15 (65.2)	0.24	0
ii) Biomedical variables						
Mean duration of diabetes, years (SD)		14.0 (8.8)	14.4 (7.9)	13.6 (9.7)	0.77	
Mean HbA1c IFCC mmol/mol (SD)		86 (27)	101 (23)	72 (22)	<0.001	2
Mean HbA1c, DCCT % (SD)		10.0 (4.6)	11.4 (4.3)	8.7 (4.2)		
Prescribed antidepressants	Yes	6 (13.0)	3 (13.0)	3 (13.0)	-	-
	No	40 (87.0)	20 (87.0)	20 (87.0)	1.0	0
Number of self-testing episodes in previous 28 days		55 [7-111.5]	20 [0-56]	100.5 [42.5-132]	0.001	1
iii) Psychological covariates						
Mean NART score (SD)		107.9 (11.3)	102.4 (11.8)	112.4 (8.6)	0.003	4
iv) Psychological predictors						
Median Beck Depression		9 [4-19.75]	18 [5.5-28]	7 [3-13]	0.066	2

Inventory score [IQR]						
Median Beck Anxiety Inventory score [IQR]		9 [4-26]	18.5 [8.5-40.3]	5 [2-11]	**0.004[c]**	1
Mean Difficulties in Emotional Regulation Scale score (SD)		84.6 (28.7)	99.7 (29.8)	72.1 (21.1)	**0.001[c]**	3
Experiences in Close Relationships Scale:						
Anxiety subscale score (SD)		61.7 (15.4)	63.7 (19.0)	59.7 (10.9)	0.39	1
Avoidance subscale score (SD)		61.3 (14.0)	63.0 (16.1)	59.7 (11.8)	0.43	1
Median Eating Disorder Examination Questionnaire score [IQR]		0.5 [0-1.4]	0.7 [0-1.9]	0.3 [0-1.2]	0.60	3
Mean Inventory of Interpersonal Problems-32 score (SD)		1.1 (0.6)	1.3 (0.6)	0.9 (0.6)	0.04	3
Median Problem Areas in Diabetes Scale score [IQR]		30 [13.8-56.3]	48.8 [19.7-77.5]	17.5 [6.3-36.3]	**0.004[c]**	1
Mean Standardised Assessment of Personality score (SD)		3.5 (2.0)	4.6 (1.9)	2.4 (1.4)	**<0.001[c]**	0

[a]Parametric continuous data are presented as mean (SD) and compared using Student's t-test; non-parametric continuous data are presented as median (IQR) and compared using Mann-Whitney *U* test; categorical variables presented as frequency (%) and compared using Fischer exact test; [c] compared to white ethnicity. Means, medians, standard deviations and quartiles are summarised to 1 decimal point, p-values are summarised to 2 significant figures.

[b]Includes part-time employment, retired or currently in education.

[c]Significant after Bonferroni correction for multiple testing (p-value <0.0055)

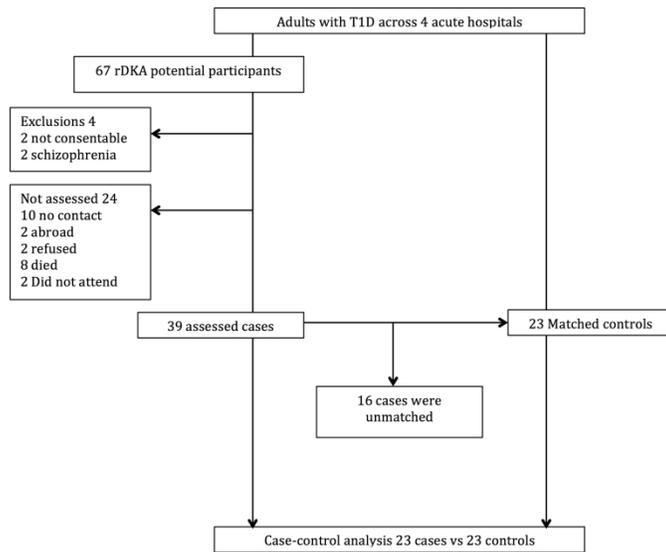Key: IQ, intelligence quotient; IQR, inter-quartile range; SD, standard deviation

Figure 1. Flow chart indicating numbers of potential recruits, those excluded and included and matching to controls

209x297mm (300 x 300 DPI)