A series of patients with hospital-acquired diabetic ketoacidosis (HADKA): a descriptive analysis

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ABSTRACT

Background

Hospital-acquired diabetic ketoacidosis (HADKA) can complicate hospital admission in people with type 1 diabetes (T1D) and type 2 diabetes (T2D). We aimed to determine the characteristics of such patients and the reasons for HADKA.

Methods

A retrospective analysis of patients referred to diabetes services with HADKA at Morriston Hospital between January 2016 and January 2022 was undertaken. Patients that were included were admitted without diabetic ketoacidosis (DKA), were aged 18 years and over, and who subsequently developed DKA in hospital.

Results

Twenty-five patients were included with a mean age of 65.2 years; nine (32.0%) were men, 13 (52.0%) had T1D and 12 (48.0%) had T2D. Patients had a mean pre-admission glycated haemoglobin of 84.7 mmol/mol, and 17 (68.0%) were insulin-treated. Most were admitted under medicine (n=14; 56.0%) and the remainder under surgery (n=11; 44.0%). More common reasons for HADKA were erroneous insulin administration (n=9; 36.0%), infection (n=7; 28.0%) and surgery (n=5; 20.0%).

Five (20.0%) patients required intensive care admission, and the mean length of hospital stay was 42.6 days (range 2–173). Three (12.0%) patients died during the hospital admission.

Conclusion

HADKA was identified in a significant number of patients at our hospital and was associated with significant mortality. Earlier recognition of ketonaemia and associated medication use may prevent HADKA and improve outcomes.

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Background

The prevalence of diabetes in the UK continues to increase at an alarming rate, with almost 4 million people diagnosed with diabetes and 1 million people are estimated to remain undiagnosed.[1] In hospital, the prevalence is greater still with one in five hospital patients diagnosed with diabetes.[2] While the vast majority of these patients are not admitted as a direct consequence of their diabetes, the condition is associated with a range of medical, surgical and psychiatric comorbidities, which ultimately means that the management of diabetes extends well beyond the diabetes team.

Over the last decade, the Joint British Diabetes Societies (JBDS) have produced numerous guidelines to support the management of people with diabetes in a range of inpatient settings. Nevertheless, when in hospital, people with diabetes are admitted an extra 1.1 days on average compared with people without diabetes.[3] While this may be a result of multi-morbidity when compared with people without diabetes, patients with diabetes frequently come to harm in hospital. Examples of clinical harm in people with diabetes include hypoglycaemia and hyperglycaemic emergencies, such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS). Previous national diabetes inpatient audits (NaDIAs) in the UK observed that around 18% and 4% of patients with diabetes admitted to hospital develop hypoglycaemia and DKA in hospital, respectively.[2] Hospital-acquired DKA (HADKA) is a life-threatening diabetes complication occurring in people admitted in hospital, though there is a relative paucity of previous studies exploring the causes and outcomes of people with HADKA.

The aim of this is study was to describe the characteristics and outcomes of patients who developed HADKA, and thereby identify patient groups more likely to develop HADKA to support preventative intervention.

Methods

This retrospective study included patients admitted to Morriston Hospital in Swansea between January 2016 and January 2022 who developed HADKA. Patients were identified retrospectively by

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diabetes specialist nurses (DSNs), and case notes and electronic records were reviewed to determine the patients' diabetes history, medications, reason for hospital admission, the precipitating cause of HADKA and their clinical outcome in hospital.

Subjects

The following inclusion criteria were used for case selection:

- developed DKA in hospital following admission for a reason other than DKA
- DKA was defined as all:
  - known diabetes or blood glucose >11 mmol/L
  - ketonaemia >3.0 mmol/L or urinary ketones >2+
  - serum pH <7.30 or bicarbonate <15 mmol/L
- referred to the DSN for inpatient review
- aged ≥18 years.

Statistical analysis

This was a descriptive case series. Discrete variables are described as number and percentage. The mean and standard deviation (SD) were used to describe continuous variables.

Results

Patient demographics

Twenty-five patients were identified with HADKA between January 2016 and January 2022 and included in this analysis. Nine (32.0%) patients were men, 16 (68.0%) were women, the mean age was 65.2 years (SD 14.6) and all patients were White. Thirteen (52.0%) patients had T1D and 12 (48.0%) had T2D with a mean duration of diabetes of 19.4 years (SD 11.7). These patients had a mean pre-admission glycated haemoglobin (HbA_{1c}) of 84.7 mmol/mol (SD 29.8) and a mean estimated glomerular filtration rate (eGFR) of 65.2 mL/min/1.73 m^2 (SD 24.5). Most patients (17 (68.0%)) were prescribed an insulin regimen, while others were prescribed alternative hypoglycaemic agents and two (8.0%) patients were treated with diet alone. The patient demographics of this cohort are presented in Table 1.

Most patients were initially admitted under general medicine (14 (56.0%)) and the remainder were admitted under various surgical teams (11 (44.0%)). The reasons for admission were varied, though more common causes for hospital admission included acute ischaemic limb (n=4), abdominal pain (n=4), general decline/frailty (n=4) and sepsis (n=3). The reasons for admission to hospital and the admitting inpatient team are presented in Fig 1. Reasons for developing HADKA included insulin administration errors (nine (36.0%)), hospital-acquired infections (seven (28.0%)) and surgery (five (20.0%)), among others. Insulin administrative errors included inappropriate insulin omission (n=6), interrupted insulin infusion (n=2) and inappropriate insulin dose reduction (n=1). These are presented in Table 2.

Patients had a mean length of stay of 42.6 days (SD 46.5), with a range of 2–173 days and a mean duration 1.4 days until resolution of DKA. At diagnosis of HADKA, patients had a mean glucose of 22.6 mmol/L, ketones of 5.4 mmol/L, pH of 7.20 and serum bicarbonate of 13.8 mmol/L. Five (20.0%) patients required treatment in the intensive care unit, and three (12.0%) patients died during the course of their hospital admission (one patient with COVID-19, one patient with bacterial pneumonia and one patient with sepsis secondary to diabetic foot infection).

Table 1. Patient demographics

Age, years, mean (SD)	65.2 (14.6)
Men, n (%)	9 (32.0)
Women, n (%)	16 (68.0)
T1D, n (%)	13 (52.0)
T2D, n (%)	12 (48.0)
Duration of DM, years, mean (SD)	19.4 (11.7)
DM medications, n (%):	
Metformin	11 (44.0)
Sulphonylurea	3 (12.0)
DPP-IV inhibitor	3 (12.0)
SGLT-2 inhibitor	4 (16.0)
Pioglitazone	0 (0)
GLP-1RA	2 (8.0)
Insulin:	17 (68.0)
basal	1 (4.0)
basal bolus	13 (52.0)
premixed	1 (4.0)
pump	2 (8.0)
HbA_{1c}, mmol/mol, mean (SD)	84.7 (29.8)
Creatinine, µmol/L, mean (SD)	92.5 (70.3)
eGFR, mL/min/1.73m^2, mean (SD)	65.2 (24.5)
Comorbidities, n (%):	
Cerebrovascular disease	3 (12.0)
Chronic kidney disease	4 (16.0)
Coronary artery disease	7 (28.0)
Lung disease	4 (16.0)
Malignancy	4 (16.0)
Peripheral vascular disease	9 (36.0)

DM = diabetes mellitus; DPP-IV = dipeptidyl-peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor analogue; HbA_{1c} = glycated haemoglobin; SGLT-2 = sodium-glucose co-transporter-2; T1D = type 1 diabetes; T2D = type 2 diabetes.

Discussion

In this retrospective analysis, the characteristics of 25 patients who developed HADKA over a 6-year period were described. Interestingly, almost half of the cases were in patients with T2D. This is an important observation as there is often a misconception around the need for insulin in people with T2D and even the risk of DKA in people with T2D. There has been a recent focus on DKA risk in people with T2D, especially in those prescribed sodium-glucose co-transporter-2 (SGLT-2) inhibitors.[5] Indeed, in this study four (16%) patients who developed HADKA were concurrently prescribed a SGLT-2 inhibitor, which may have contributed to these patients developing HADKA, though only one (4%) case was attributed to this in the case notes (see Table 2).[5] Moreover, with

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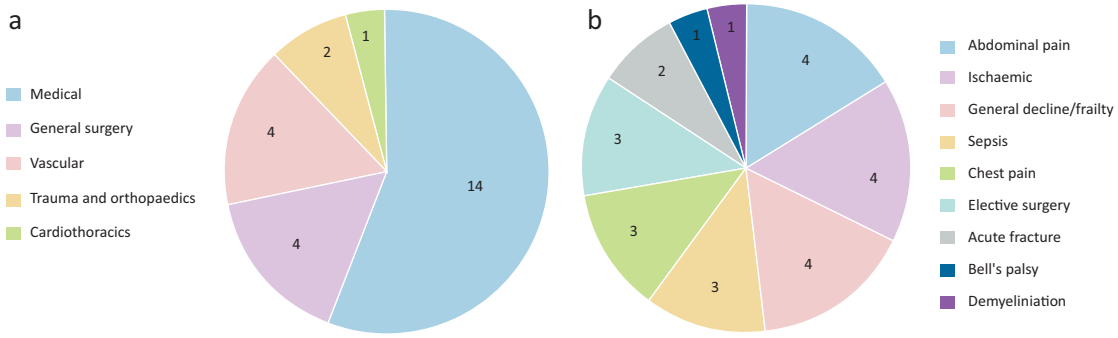

Fig 1. Inpatients that developed hospital-acquired diabetic ketoacidosis. a) The hospital team under which the patient was admitted. b) The initial reason for hospital admission.

increasing T2D duration, pancreatic beta cell function declines and so patients have a greater risk of hyperglycaemic emergencies, such as DKA and HHS with their relative insulinopenia.[6] The risk of DKA is greater still in those with higher HbA_{1c}, suggestive of poor glycaemic control and insulin deficiency.[7] Indeed, the patients presented in this study had a high mean pre-admission HbA_{1c} of 84.7 mmol/mol suggestive of an at-risk population.

In our cohort, the most common reason for developing HADKA were errors of insulin administration, including omission (six (24.0%)), inappropriate dose reduction (one (4.0%)), and interrupted insulin infusions (two (8.0%)). These are events that should never happen in hospital, and there are an increasing number of UK guidelines and resources available to support inpatient clinical teams in the management of patients with diabetes in a range of settings. During periods of sickness, there is a hormone response (including secretion of endogenous glucocorticoids, adrenaline and glucagon) that drives gluconeogenesis, often resulting in ketone formation. In people with T1D or advanced stages of T2D, the insulin response is frequently insufficient to regulate ketone formation and DKA may occur.[8] Such patients often require initiation or dose escalation of insulin, though sometimes insulin is inappropriately held or the dose is reduced if, for example, the patient is not eating or drinking.[8] Improving the awareness of doctors and nurses who are involved with the inpatient care of people with diabetes of the guidelines produced by the JBDS for the management of inpatients with diabetes would likely reduce the incidence of HADKA and other serious or life-threatening diabetes-related adverse clinical events, which are available on the JBDS website.[9]

Table 2. Causes of hospital-acquired diabetic ketoacidosis

Insulin errors, n (%):	
Omission	6 (24.0)
Dose reduction	1 (4.0)
Interrupted infusion	2 (8.0)
Infection, n (%)	7 (28.0)
Surgery, n (%)	5 (20.0)
SGLT-2 inhibitor, n (%)	1 (4.0)
Steroid use, n (%)	1 (4.0)
Enteral feeding, n (%)	1 (4.0)
Cardiac event, n (%)	1 (4.0)

SGLT-2 = sodium-glucose co-transporter-2.

To date, we are aware of just one previous study exploring the incidence and causes of HADKA, undertaken at an Australian centre.[10] In that study, 12 patients with HADKA were identified across two centres over a 4-year period, with DKA defined as a pH of ≤7.3, bicarbonate of ≤18 mmol/L and positive ketones (urine or plasma). In this group, most patients (75%) had T2D with a mean HbA_{1c} of 68 mmol/mol. Most patients (83.3%) required intensive care admission, and 16.6% of patients in this cohort died. The results from our cohort are similar, except fewer patients required intensive care admission compared with this Australian study (20.0% vs 83.3%). Our findings add significantly to these previous observations as a more stringent definition of DKA was applied in our cohort, a greater number of patients were included and this is the first description of a UK-based group of patients with HADKA that we are aware of. In the UK, the NaDIA has previously observed a consistent prevalence of HADKA at around 4%.[2] However, the causes of HADKA were not described by the NaDIA at a national level and the group suggest that, for each event, a serious incident is reported and a root-cause analysis should be undertaken.

A significant proportion of this group (20.0%) required intensive care admission, and the length of hospital stay in the cohort was also significant. This highlights the associated economic burden of HADKA on healthcare resources at a time when such resources are increasingly precious. Of course, the major mortality associated with HADKA in our cohort (and in previous cohorts) may reflect these patients' general condition and the concurrent illness that precipitated the development of HADKA.[10] Indeed, while DKA did not appear to directly cause death in these patients, its occurrence naturally reflects the severity of their underlying sepsis and comorbidity.

Moving forward in our practice, improving the awareness of clinicians involved with the treatment of people with diabetes in hospital is important; for example, highlighting recent JBDS guidelines to medical and nursing staff for patients undergoing surgery, enteral feeding, long-term steroid treatment and general sickness is important. Additionally, given the recent focus on SGLT-2 inhibitor-associated DKA, it is essential to highlight the

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need to review these medications and likely hold during periods of illness.[5,11] Of course, clinician education by diabetes specialist teams to reiterate the absolute need to give insulin to people with T1D is needed, and to be cautious with withdrawal or omission of insulin in people with T2D who are admitted with significant concurrent illness, or the risk factors described earlier, because insulin requirements generally increase in times of significant illness to counteract the catabolic state associated with the stress hormone response. Locally this has been achieved through updating and adding to local guidelines in keeping with the JBDS updates, formal and informal teaching to medical and nursing teams in various inpatient specialties, and presenting these data at local meetings.

Given the high prevalence of diabetes in hospitalised patients, inpatient review of all patients with diabetes is not usually possible on a routine basis. However, clinicians should always consider referring patients with complex medical issues or severe non-diabetes-related illness to the diabetes team to support diabetes management, if concerned, and prevent life-threatening inpatient complications, such as HADKA. Further guidance to support inpatient teams in a number of settings is available from the JBDS.[9]

Conclusion

To our knowledge, this is the first descriptive series of patients with HADKA in the UK. HADKA is a preventable, life-threatening, hospital-acquired complication that was associated with significant mortality and inpatient hospital stay in our cohort. Educational interventions for all staff who treat people with diabetes in a range of inpatient settings is needed, given the wide range of inpatient clinical areas and causes of HADKA that were observed in this study. Further, larger-scale observational studies to corroborate our findings would be of interest and may support further targeted intervention to prevent this critical diabetes complication. ■

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