Review

The impact of diabetic ketoacidosis on cognitive function and its importance in forming prevention strategies

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Abstract

Diabetic ketoacidosis (DKA) is a potentially serious complication of diabetes that emerges following an absence of insulin, and prevalence is rising. As such, clinicians have a responsibility to recognise patients that might be at higher risk of DKA and implement preventative strategies wherever possible. Given that diabetes has a heavy self-care burden, having adequate cognitive functioning (CF) is essential to preserve good health and minimise DKA episodes. DKA has been associated with acute cognitive impairments within specific domains and recurrent episodes may even successively further reduce CF. Changes in CF should be considered in the long-term management of diabetes, especially for older patients who are at greater risk of DKA recurrence. Diabetes-management education programmes might benefit from implementing different modes of delivery for individuals with reduced CF or considering DKA-specific programmes for these patients. Suitable support plans can potentially reduce the incidence of DKA, thus, benefitting public health.

Abbreviations

CF - Cognitive function
DKA - Diabetic ketoacidosis
EF - Executive function
NAA - N-acetylaspartate
PSE - Psychomotor efficiency
T1D - Type 1 diabetes

Introduction

Since 1996, the prevalence of diabetes in the UK increased from 1.4 million to 3.5 million patients.[1] Diabetic ketoacidosis (DKA) is a serious complication of diabetes following an absolute absence of insulin, predominantly affecting type 1 diabetes (T1D) patients.

> *In recent years, the incidence of DKA in T1D patients at initial diagnosis has increased from 35% in 2007 to 58% in 2018.[2]*

Therefore, there is a responsibility imposed upon clinicians to recognise patients who might be at a higher risk of DKA and implement preventative strategies wherever possible. Given that diabetes has a heavy self-care burden, having adequate cognitive functioning (CF) is essential to preserve good health and minimise DKA episodes. There is some evidence to suggest that DKA is linked to reductions in CF. Poor CF may impact a patient's ability to self-care and increase risk of DKA episodes.

What is DKA?

> *Characteristic presentations of DKA are hyperglycaemia, ketonaemia and metabolic acidosis.*

DKA is most commonly caused by poor concordance with insulin therapy often after initial T1D diagnosis or following infections of the chest/urinary tract.[3] Insulin deficiency prevents the uptake of glucose into metabolic tissues, which results in hyperglycaemia.[3] This forces tissues to rely on other sources of energy such as triglycerides and

amino acids, which form ketones as a by-product of metabolism.[3] Prolonged insulin absence causes a build-up of ketones in the blood, which results in metabolic acidosis. DKA may induce symptoms of polyuria, vomiting and abdominal pain. Additionally, it has been shown that patients of all ages demonstrate changes in their CF.[2,4] DKA can be accompanied by confusion, loss of consciousness and cerebral oedema,[3] further reinforcing that DKA may influence neurological functioning within the brain.

Why is it important to understand the link between DKA and CF?

CF can be greater conceptualised by differentiation into functional domains - some key areas being attention, executive function and memory.[5] Impairment within any domain may impact an individual's ability to lead an independent life. Diabetic patients have an arduous self-care obligation, of which responsibilities include daily monitoring of blood glucose and taking insulin at the correct dose and time.[6] Poor CF has the potential to decrease adherence to insulin therapy. Hence, a vicious cycle can emerge of DKA reducing CF, a resultant worsening of diabetes self-management and thus increased likelihood of DKA incidence.

Previous DKA is a known risk factor for recurrence - approximately 20% of people who experience DKA at the time of initial T1D diagnosis might experience sequential episodes.[2] In older adults, the risk of experiencing another DKA episode is even greater at 34%.[2] As the life expectancy of T1D patients increases, there is an increasing population of older adults living with the disease, which may help to explain why a higher number of older adults are experiencing successive DKA events.[2] The normal ageing process has shown links with declining CF.[7] When combined with the greater risk of mortality that older DKA patients face following an event,[8] diabetics within this age group appear to be particularly vulnerable to poor health outcomes.

> *Gaining a better understanding of the cognitive impact following DKA might lead to more effective management plans, especially for the most high-risk patients.*

This review will consider which areas of CF are most impacted following DKA, and how DKA recurrence and age might affect prognosis. Some ideas to help reduce the onset of DKA will also be explored. Gaining a better understanding of how cognitive states may be impacted by DKA could aid clinicians in creating an effective management plan to reduce recurrence and severity of episodes in diabetic patients.

Which specific areas of cognition are affected in DKA?

Executive function (EF) is an important measure of CF. It refers to a group of skills, such as attentional control and task-planning, that are needed to coordinate cognitive processes to achieve a common goal.[9] Impairments in EF can affect an individual's ability to complete daily routines. This might lead to difficulty for patients in keeping to a schedule of diabetes management. Children with a history of DKA have shown lower EF than their age-matched counterparts, with higher glycated haemoglobin correlating with lower CF.[4] This suggests that poor glycaemic control directly affects CF. These results have been replicated in older adults (mean age = 67), who showed significantly reduced CF, especially within EF and psychomotor efficiency (PSE).[2] PSE describes the overall speed and coordination of the cognitive system. It is an important factor to consider since changes to information processing abilities may create feelings of being overwhelmed, which can be expressed as distress or anxiety. These emotional consequences are likely to have an impact on the extent to which an individual is able to carry out self-care.

It is imperative to note that the previously mentioned studies on older adults and children[2,4] did not have long-term follow-up aspects, so it is unclear as to how long the reduced cognitive states presenting at the time of the study would persist. A study performed on T1D adults showed that higher glycated haemoglobin was linked to acutely reduced PSE, however, there were no long-term declines in CF.[11] These patients also experienced successive severe hypoglycaemic episodes, which further emphasises the idea that poor glycaemic control is associated with cognitive difficulties, but the direct effect of hyperglycaemia on the participants is not clear. Moreover, this study considered DKA in the context of T1D, which although common to most DKA patients, is not an exclusive feature and so long-term studies specific to broader DKA patients is required.

Does frequency of DKA affect CF?

There is evidence to suggest that repeated DKA may lead to progressively greater neurological injury, which may in turn affect CF.[12] A case study following an adolescent T1D patient found that recurring DKA was linked to reduced N-acetylaspartate (NAA).[12] NAA is a neurological marker which is affected by decreased neuronal function or neuronal loss.[12] This indicates that DKA directly impacts the structural integrity of neurons. Although NAA levels did not return to prior baseline levels, there was some recovery shown in readings taken 3 days after the episode, which suggests that the time period acutely following DKA is crucial to ensure maximum neuronal recovery. Total recovery was greater following the first episode, indicating that with successive DKA episodes the extent of recovery diminishes. Neurocognitive testing was not performed in this study, so it is not possible to delineate how DKA may have affected CF.

A study following an older cohort, found that those with recurrent episodes were 3.3 times more likely to have lower CF than those who had never experienced DKA.[2] This study only considered DKA which resulted in hospitalisation; DKA that is less serious in nature might not have as great an effect on CF. Moreover, recurrent DKA in older patients, especially of the nature that requires hospitalisation, might have more extreme consequences than in younger patients. Further research will be necessary to gain a better understanding of the effect of repeated DKA episodes on CF in a wider demographic.

The impact of age on DKA incidence

Normal ageing is associated with lower CF in healthy patients,[13] so in older DKA patients the rate of decline may be further exacerbated. Moreover, older populations have a higher risk of experiencing repeated episodes.[2] Successive insult to CF following recurrent DKA might further impose difficulties in effectively self-managing their diabetes and preventing future DKA. Patients within this age group are more likely to experience DKA-related hospitalisations, which could be due to health fragilities that can accompany old age. With older age comes greater likelihood of experiencing multiple comorbidities,[8] which is likely to increase risk of complications. Moreover, patients managing multiple comorbidities are often burdened with polypharmacy. Managing multiple medications alongside insulin could be challenging to individuals, especially if cognitively impaired. These factors may all contribute to the greater risk of DKA-related mortality within older populations.[8] Comorbidities, ability to self-care and CF all need to be considered by clinicians when implementing DKA prevention methods for this age group.

Whilst older populations are at greater risk of recurring and more serious DKA, young adults have been observed to experience more singular DKA episodes.[4] Young adults are more likely to experience mental health challenges, to use tobacco and less likely to see a primary care provider than older adults – these are all contributing factors for poor glycaemic control.[14] These are largely modifiable risk

factors, so perhaps greater knowledge of how lifestyle factors impact diabetes could help to reduce DKA incidences in this age cohort. Eating disorders are a lesser known risk of DKA. Diabulimia is the colloquial term for a specific eating disorder affecting T1D patients, especially young females.[15] These patients might knowingly omit insulin with the goal of weight loss, and as a result may experience DKA. Encouraging clinicians to include psychological evaluations alongside routine physical examinations of diabetic patients may improve diabulimia recognition. Appropriate psychological interventions may help to prevent avoidable DKA episodes in these patients.

Preventing DKA

Ensuring that patients receive appropriate care could reduce the risk of DKA events. Personal modifications to patient care, such as home visits for those experiencing difficulty in attending GP appointments, could improve wider access to healthcare. This may be especially relevant as fragmentation of healthcare is associated with greater risk of recurrent DKA.[8] A report evaluating DKA management from patient perspectives found that "prevention of recurrent episodes" was important for patients. Additionally, "providing information for what to expect over the course of treatment for diabetic ketoacidosis" was considered a good step for reducing their anxieties and fears.[16] As such, patients might also benefit from a clear breakdown of what to expect at their initial diagnosis of diabetes in order to reduce anxieties - this might be helpful in individuals prone to feeling overwhelmed. Given that elevated glycated haemoglobin is linked to reduced PSE,[10] which itself is associated with feeling overwhelmed, this might be especially relevant for diabetic patients that struggle with glycaemic control.

> *Diabetes self-management education can give patients relevant knowledge to prevent recurrent DKA.*

Emphasis should be placed on tackling unexplained hyperglycaemia and ketosis at home, which can emerge when patients get unwell with other illnesses - this is known as sick day management.[16] Many patients perceive this as an important category to help them feel better about managing their condition.[16] Improved knowledge on how to manage their condition has been associated with reduced hyperglycaemia, enhanced treatment adherence and improved abilities in using technological devices such as insulin pumps.[17] Indeed, structured education programmes have been shown to reduce DKA hospitalisations.[6]

Various diabetes education courses currently exist within the UK,[18] but access may be gated behind clinical referral or socioeconomic factors. Furthermore, DKA patients might have already participated in a programme at the time of their T1D diagnosis and feel they no longer need to be educated on how to manage their condition. There do not appear to be specific programmes for those who have previously experienced DKA, so perhaps arranging such schemes could be valuable. Moreover, DKA patients with reduced CF may benefit from different forms of educational delivery to make the information more accessible - this is something clinicians should consider when forming management plans. When CF is impaired so significantly that educational programmes are ineffective, further support might need to be explored, such as district nurses who can provide in-home care and administer insulin themselves.[19]

Conclusion

At present, the literature regarding DKA and CF remains relatively sparse. Whilst DKA has been associated with acute cognitive impairments, most notably in EF and PSE, the long-term effects remain unclear. DKA episodes might be more common in younger patients but older cohorts have a greater risk of mortality - these age cohorts might require additional care in managing their diabetes to prevent episodes.

There is some evidence that recurrent episodes can successively further reduce CF. This needs to be considered by clinicians, especially for older patients who are at greater risk of recurrence. Structured diabetes-management education programmes have been shown to reduce DKA episodes and improve patient satisfaction. Different modes of delivery might be appropriate for those that are unable to engage with these programmes due to, for example, low CF. Moreover, the introduction of DKA-specific programmes may prove more efficacious within DKA patients. Suitable support plans can potentially reduce the incidence of DKA, thus, benefitting public health.

Acknowledgements I would like to thank the University of Exeter for supporting me in writing this article, especially my supervisor Dr Alice McLoughlin for helping me better understand the disease profile of diabetes.

Contribution statement The author made substantial contributions to the article and was responsible for drafting the work. The author gave approval for the article to be included in Inspire.

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