The incidence of diabetic ketoacidosis associated with empagliflozin use in Aotearoa New Zealand: a preliminary review

Lynne Chepulis, An Yu, Ryan Paul

Diabetic ketoacidosis (DKA) is a life-threatening but largely preventable complication of diabetes, resulting from excess ketone production due to relative or absolute insulin deficiency.[1] DKA is primarily associated with type 1 diabetes mellitus (T1D), but may also occur in end-stage type 2 diabetes mellitus (T2D),[2] and in those treated with sodium-glucose cotransporter-2 inhibitors (SGLT2).[3] SGLT2 are a relatively new class of oral glucose lowering therapies that are recommended as second or third line agents in the management of T2D given they typically lead to weight loss, do not cause hypoglycaemia alone, and are effective agents in the secondary prevention of cardiovascular and renal disease independently of their effect on glucose levels.[4,5] DKA is a rare adverse effect of SGLT2 due to the "switch" to fatty acid metabolism, reduced urinary excretion of ketones, and increased glucagon secretion.[6] The diagnosis of DKA associated with SGLT2 use is often delayed, as glucose levels are typically normal or only mildly elevated at <14mmol/L (known as euglycaemic DKA),[6] and a lack of resources for patients to self-monitor their capillary ketone levels at home. Therefore, the focus is on reducing the risk of DKA by withholding SGLT2 in acute illness and prior to elective procedures, and on not using SGLT2 in any conditions that predispose to ketosis such as prolonged fasting, low carbohydrate or "ketogenic" diets, increased alcohol intake, and insulin deficient states such as T1D and end-stage T2D.[7]

Empagliflozin is the only funded SGLT2 in Aotearoa New Zealand, and became available from 1 February 2021 under special authority criteria. International trial data suggests that the incidence of DKA associated with empagliflozin in T2D is between 0.6% and 2.2% (6–2.2 per 1,000 patient-years),[8,9] but real world studies suggest that the incidence may be higher. Given the recent introduction of empagliflozin in Aotearoa New Zealand, the incidence of DKA associated with empagliflozin in this population is not known. Moreover, the national rollout of empagliflozin in the absence of "traditional" second to third line agents such as GLP1 receptor agonists, provides a unique opportunity to investigate the real-world incidence of DKA in new empagliflozin users. Thus, the aim of this study was to provide a preliminary review of DKA associated with empagliflozin use in Aotearoa New Zealand.

Retrospective data were collected from the National Pharmaceutical dataset for all patients prescribed empagliflozin between February and October 2021. These data were then linked by NHI (National Health Index number) to the National Minimum dataset (February 2021–March 2022), and admissions for DKA were recorded. A DKA admission was deemed to be associated with empagliflozin if it occurred within the time covered by dispensed medication, allowing for a medication possession ratio of 0.8 (eg based on 80% medication use, a 90-day prescription can last up to 112.5 days).[10] DKA incidence was then reported by age group, gender, DHB and ethnicity. Data were linked and analysed using R software, and specific subgroups were compared using Chi-squared analyses, with a significance level of 0.05.

During the nine month period, there were 167 admissions for DKA in 40,523 patients prescribed empagliflozin, but only 94 admissions were temporally associated with empagliflozin use (92 individual patients) giving an overall incidence of 0.23% or 2.3/1000 patient years. DKA admissions were at least two-fold more common in NZ Europeans (0.35%) than in Māori (0.17%), Pacific (0.18%) or Asian (0.10%) patients (all $P \leq 0.01$) with no other significant differences observed between other groups (Table 1). The relative risk of having an empagliflozin associated DKA event for NZ Europeans was found to be 2.25 times that of non-Europeans (95% CI 1.48–3.41). The median

age at DKA admission was 60.5 years, with the highest incidence occurring in those aged <30 years (0.75%) compared to 0.17%–0.25% in those aged >30 years (Table 1; all P ≤0.01). There were no significant differences in DKA admissions between sexes (0.26% vs 0.19%; 95% CI 0.89–2.10) or between the 15 DHB regions (incidence range 0–0.54%) affected (P >0.05 for both).

Caution needs to be applied to these data given the small numbers and the fact that we have not reviewed empagliflozin use by clinical indication or alongside other diabetes medications (eg insulin), but our conservative estimate of the incidence of DKA associated with empagliflozin use in Aotearoa New Zealand appears similar to other real world studies.[8,9] However, the 5–10-fold higher incidence of DKA with empagliflozin use in real world studies than in clinical trials, highlights the importance of providing sick day management advice and avoiding empagliflozin in high-risk groups. In particular, our study indicates that NZ European patients with T2D demonstrated higher DKA rates, and this needs to be explore further as it is unknown if this is due to the small study numbers, misdiagnosis of the diabetes type (given that T1D and pancreatogenic diabetes are more common in NZ Europeans) and/or additional factors such as the use of ketogenic diets. Further, with the limitations of the data in this study it not possible to identify the predisposing factors for each presentation so it is not known how many admissions were potentially "preventable". However, even if case reviews determined that all 167 cases in this study were linked to empagliflozin use, DKA is still a rare adverse effect.

The finding that DKA with empagliflozin use is less common in Māori and Pacific peoples is somewhat surprising, given they represent approximately half the patients dispensed empagliflozin in Aotearoa New Zealand thus far and the well-established inequities in this group.[11] However, it is important to note that Māori and Pacific peoples are less likely to access healthcare in New Zealand,[12] so episodes of mild DKA may have not presented in this group. Further, all DKA admissions in those less than 30 years of age were in Māori or Pacific peoples, likely highlighting the greater prevalence, progression and severity of T2D, its complications and co-morbidities at a younger age in Māori and Pacific peoples than in other ethnicities.[13] Indeed, in addition to the lower insulin use, the better tolerability of persistent empagliflozin use, and/or more at-risk behaviours in this age group, the greater progression and severity of T2D in emerging adults may explain the higher risk of DKA found with empagliflozin in this age group.[14] But, our data should allay some fears of using empagliflozin in older adults and in Māori and Pacific peoples, who have the most to benefit from empagliflozin since they have the greatest burden of cardiovascular and renal disease; although, as per national guidelines, we would still recommend caution in using empagliflozin in patients over 75 years of age and in insulin-deficient emerging adults.[5] The addition of the special authority clauses of Māori or Pacific ethnicity and onset of diabetes at a young age to increase access to empagliflozin was controversial to some given the benefit and safety of empagliflozin in these populations is largely unknown, as previous studies were designed to predominantly assess cardiovascular safety and superiority in older Caucasian populations. Any benefits and clinical indicators for prescribing of empagliflozin cannot be determined from our data, but the greater use of empagliflozin and lower risk of DKA in Māori and Pacific peoples suggests that the SA clause is increasing access, and importantly, is not causing harm. However, further work is required to definitively assess the effects of the SA clauses on access to empagliflozin and potential other harm, such as the genitourinary adverse effects.

In conclusion, the incidence of DKA associated with empagliflozin use in Aotearoa New Zealand appears similar to other real world studies, remains rare and older adults and Māori and Pacific peoples do not appear to be at greater risk. However, further work is required to explore the impact of age, ethnicity and clinical risk on the incidence of DKA with empagliflozin.

Table 1: Characteristics of diabetic ketoacidosis (DKA) associated with empagliflozin use in patients with Type 2 diabetes

Ethnicity	All empaglifozin users	Total DKA patient admissions[1]	DKA admissions by age (years)							
		Number	Median age	<30 (n=668)	31-40 (n=2,282)	41-50 (n=5,751)	51-60 (n=11,185)	61-70 (n=12,239)	70+ (n=8,398)	75+ (n=4,562)
All[1]	40,523	92 (0.23%)[a]	60.5 (SD= 14.17)	5 (0.75%)[a]	5 (0.22%)[b]	10 (0.17%)[b]	26 (0.23%)[b]	31 (0.25%)[b]	15 (0.18%)[b]	11 (0.24%)[b]
NZ European	15,673	55 (0.35%)[b]	64	0	2 (0.6%)	2(0.2%)	17 (0.5%)	20 (0.4%)	14 (0.3%)	11 (0.3%)
Māori	10,188	17 (0.17%)[b]	52	2	1 (0.1%)	5 (0.3%)	6 (0.2%)	3 (0.01%)	0	0
Pacific	8,157	15 (0.18%)[b]	55	3	2 (0.3%)	2 (0.1%)	3 (0.1%)	4 (0.2%)	1 (0.1%)	0
Asian	4,725	5 (0.1%)[b]	65	0	0	1 (0.1%)	0	4 (0.3%)	0	0
Other	2,780	0	N/A	0	0	0	0	0	0	0

[1] Differing superscript letters between subgroups denote statistical significance (P ≤ 0.05).

COMPETING INTERESTS
Dr Ryan Paul has previously received speaker's fees from both Boehringer Ingelheim and Eli Lilly who supply empagliflozin in Aotearoa New Zealand.

AUTHOR INFORMATION
Lynne Chepulis: Waikato Medical Research Centre, University of Waikato, Hamilton; Te Huataki Waiora School of Health, University of Waikato, Hamilton.
An Yu: Te Huataki Waiora School of Health, University of Waikato, Hamilton.
Ryan Paul: Waikato Medical Research Centre, University of Waikato, Hamilton; Waikato Regional Diabetes Service, Waikato District Health Board, Hamilton.

CORRESPONDING AUTHOR
Lynne Chepulis: Waikato Medical Research Centre, University of Waikato, Hamilton; Te Huataki Waiora School of Health, University of Waikato, Hamilton. Medical Research Centre, University of Waikato, Private Bag 3015, Hamilton. Lynnec@waikato.ac.nz

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