# Management & prevention of type 2 diabetes

## Diabetic ketoacidosis and sodium–glucose cotransporter 2 inhibitors

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The European Medicines Agency (EMA) has begun a review of the risk of diabetic ketoacidosis (DKA) associated with the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors (EMA, 2015). This was triggered by the European surveillance system, which received 101 reports of DKA after approximately 0.5 million patient-years of use. One unusual facet of the cases reported was that often the glucose levels were only moderately elevated. The Food and Drug Administration (FDA) in the USA has recently issued an alert after their database identified 20 cases of DKA in people being treated with SGLT2 inhibitors (FDA, 2015). Factors identified in some of the reports as potential triggers for DKA included major illness, reduced food and fluid intake and reduced insulin dose (Redford et al, 2015).

Two articles published this quarter provide more information on this subject. The paper by Peters et al (summarised alongside) is a 13-episode, 9-patient case series obtained by the author contacting colleagues in the USA. Seven of the patients described had type 1 diabetes (five of whom were using insulin pumps) and two had type 2 diabetes. Plasma glucose measurements at presentation varied from 6.9 to 12.4 mmol/L. The authors say that the most important feature is that the individuals did not recognise they had DKA as their glucose levels were not high, so instead of increasing insulin doses, insulin dose was unchanged or decreased. When the patients presented for acute medical care, their providers often failed to recognise the DKA. All the patients responded readily to intravenous fluids and insulin. Potential contributors to the DKA in those with type 1 diabetes were concomitant infection, increased activity or reduced food intake coupled with acute insulin dose reduction or omission.

The paper by Erondu et al (summarised on the next page) is an analysis of DKA events in 17 586 people with type 2 diabetes from randomised controlled studies of the SGLT2 inhibitor canagliflozin. There were DKA events reported in 12 individuals: 10 in the canagliflozin group and two in the comparator group. Most individuals with DKA had a blood glucose greater than 13.9 mmol/L, were on insulin and had DKA-precipitating factors, including six who had evidence of autoimmune diabetes (type 1 diabetes or latent autoimmune diabetes of adulthood [LADA]).

They postulate that people diagnosed as having type 2 diabetes or misdiagnosed as having type 2 diabetes (e.g. LADA, type 1 diabetes) and who have a low beta-cell reserve, coupled with a potential SGLT2 inhibitor-associated increase in glucagon, are unable to produce sufficient insulin to suppress hepatic ketogenesis and peripheral lipolysis, which in the setting of an acute illness (and associated increase in insulin resistance) can develop DKA.

Type 1 diabetes is not a currently approved indication for SGLT2 inhibitors, and so the use of these agents in many of the patients described in the paper from Peters et al is "off" licence. The issue of DKA associated with SGLT2 inhibitors is currently the subject of much interest from researchers and medicines agencies.

While further advice from these is awaited, it is recommended that individuals taking SGLT2 inhibitors should be assessed for ketoacidosis when they present with signs or symptoms of metabolic acidosis in order to prevent delayed diagnosis and management. ■

EMA (2015) *Review of diabetes medicines called SGLT2 inhibitors started.* EMA, London. Available at: http://bit.ly/1GQl3am (accessed 20.10.15)

FDA (2015) FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. FDA, Silver Spring, MD, USA. Available at: http://1.usa.gov/1H6Xf2a (accessed 22.10.15)

Redford C, Doherty L, Smith J (2015) SGLT2 Inhibitors and the risk of diabetic ketoacidosis. *Practical Diabetes Int* **32**: 263–4a

**Diabetes Care**

## euDKA and SGLT2 inhibitors

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| Readability | ✓✓✓✓✓ |
| Applicability to practice | ✓✓✓✓✓ |
| WOW! Factor | ✓✓✓✓✓ |

1 Sodium–glucose cotransporter 2 (SGLT2) inhibitors have recently been linked to an increased risk of euglycaemic diabetic ketoacidosis (euDKA).

2 The authors identified cases incidentally by contacting collaborators to see if they had observed similar cases to the authors.

3 Across the USA, 13 episodes of SGLT2 inhibitor-associated euDKA were identified in nine individuals (seven with T1D and two with T2D).

4 The absence of significant hyperglycemia in these individuals delayed recognition of ketoacidosis for patients and healthcare professionals.

5 Those with T1D were prescribed SGLT2 inhibitors off-label, although they are currently being trialled in people with T1D.

6 SGLT2 inhibitors seem to be associated with euDKA and ketosis, perhaps as a consequence of their non-insulin-dependent glucose clearance, hyperglucagonemia and volume depletion.

7 The authors conclude that DKA can occur in the setting of relative euglycaemia so being able to recognise the symptoms is important for all. Education and awareness of the symptoms of DKA is paramount. Individuals with T1D and T2D who experience nausea, vomiting, shortness of breath, or malaise while taking an SGLT2 inhibitor should be promptly evaluated for urine or plasma ketones at home or in a medical setting, even if glucose levels are nearly normal.

Peters AL, Buschur EO, Buse JB et al (2015) Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium–glucose cotransporter 2 inhibition. *Diabetes Care* **38**: 1687–93

## Diabetes Care

### DKA occurrence from canagliflozin trials

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| Readability | ✓✓✓✓ |
| Applicability to practice | ✓✓✓✓✓ |
| WOW! Factor | ✓✓✓✓✓ |

1 Using data from completed and ongoing randomised studies of canagliflozin, the authors assessed the serious adverse events of diabetic ketoacidosis (DKA) and related events (ketoacidosis, metabolic acidosis and acidosis) among over 17 500 people, comprising nearly 24 000 patient-years of data. The mean exposure to canagliflozin was 1.4 years.

2 Serious adverse events of DKA and related events were reported in 12 individuals: four, six and two treated with canagliflozin 100 mg, 300 mg and comparator, respectively.

3 Most individuals with DKA and related events had a blood glucose >300 mg/dL (16.7 mmol/L) at presentation of DKA, were on insulin and had DKA-precipitating factors, including some with misdiagnosed type 1 diabetes or latent autoimmune diabetes of adulthood.

4 In this study, the incidence of DKA was consistent with limited existing observational data in the general population with type 2 diabetes.

Erondu N, Desai M, Ways K, Meininger G (2015) Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. *Diabetes Care* **38**: 1680–6

## BMJ

### Systematic review: Type of fats and health risk

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| Readability | ✓✓✓ |
| Applicability to practice | ✓✓✓✓✓ |
| WOW! Factor | ✓✓✓✓✓ |

1 A systematic review and meta-analysis was carried out to review the association between intake of saturated fat and trans unsaturated fat and all-cause mortality, cardiovascular disease (CVD) and associated mortality, coronary heart disease (CHD) and associated mortality, ischaemic stroke and type 2 diabetes.

2 Forty-one observational, primary reports investigating the associations of saturated fat or trans unsaturated fat or both (total, industrially manufactured, or from ruminant animals) with all-cause mortality, CHD/CVD mortality, total CHD, ischaemic stroke or type 2 diabetes were included.

3 Saturated fats were found not to be associated with the above health risks, but the evidence is heterogeneous. Trans fats are associated with increased mortality rates compared to saturated fats, which could be due to the higher level of industrial trans fat than ruminant-derived trans fats.

de Souza RJ, Mente A, Maroleanu A et al (2015) Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ* **351**: h3978

## Diabetes Res Clin Pract

### Sulphonylurea use in nursing home residents

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| Readability | ✓✓✓✓ |
| Applicability to practice | ✓✓✓✓ |
| WOW! Factor | ✓✓✓✓ |

1 The aim of the study was to examine the extent to which sulphonylurea (SU) use is associated with fractures and falls among long-stay nursing home residents in the USA with T2D.

2 The authors conducted a propensity-matched retrospective new user cohort study, comprising 5807 people taking an SU and 6151 people taking a biguanide initiated as a monotherapy after entry into the nursing home. Hospitalisation records were used to identify hypoglycaemia events and fractures.

3 Falls were fairly common in this population – 37.4 per 100 person-years. Initiation of an SU was not associated with fractures but was associated with a risk of falls among residents with moderate limitations to daily living (adjusted hazard ratio, 1.13 [95% confidence interval, 1.00–1.26]). Those with minimal physical limitations or dependance did not have an increased risk of falls or fractures.

Lapane KL, Jesdale BM, Dubé CE et al (2015) Sulfonylureas and risk of falls and fractures among nursing home residents with type 2 diabetes mellitus. *Diabetes Res Clin Pract* **109**: 411–9

## Ann Intern Med

### Diet and physical activity programmes

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| Readability | ✓✓✓ |
| Applicability to practice | ✓✓✓✓ |
| WOW! Factor | ✓✓✓✓ |

1 A systematic review of the efficacy of diet and physical activity promotion programmes for people at increased risk of T2D to reduce diabetes risk, decreased body weight and glycaemia was carried out.

2 Fifty-three studies evaluating 66 programmes were identified. Some compared the programmes to usual care, or a less intensive intervention or did not have a comparator.

3 The programmes included were highly heterogeneous (residual $I^2$=95%).

4 Compared with usual care, the diet and physical activity promotion programmes reduced T2D incidence, decreased body weight and fasting blood glucose level, and improved other cardiometabolic risk factors.

5 Combined diet and physical activity programmes were concluded to be effective in reducing new-onset diabetes, with more intensive interventions appearing to be more effective.

Balk EM, Earley A, Raman G et al (2015) Combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: A systematic review for the community preventive services task force. *Ann Intern Med* **163**: 437–51

> *"Combined diet and physical activity programmes were concluded to be effective in reducing new-onset diabetes, with more intensive interventions appearing to be more effective."*