How can the selection of patients with type 1 diabetes suitable for adjunctive treatment with SGLT inhibitors be optimized?

SGLT, sodium-glucose co-transporter

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How can we select patients for adjunctive therapy with SGLT2 inhibitors and mitigate against adverse events?

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SGLT, sodium-glucose co-transporter

Selecting patients for adjunctive therapy with an SGLT inhibitor[1,2]

Before initiation:

- >18 years
- Assessed for DKA risk factors
- Willing and able to monitor ketone levels regularly
- Normal ketone levels
- Several baseline ketone readings 1–2 weeks prior; is familiar with how behaviours and circumstances affect these levels

At initiation:

- Received education on the risk of DKA, how to recognize DKA risk factors and appropriate actions
- Underwent correction of volume depletion if required
- eGFR ≥60 ml/min/1.73 m^2
- BMI ≥27 kg/m^2

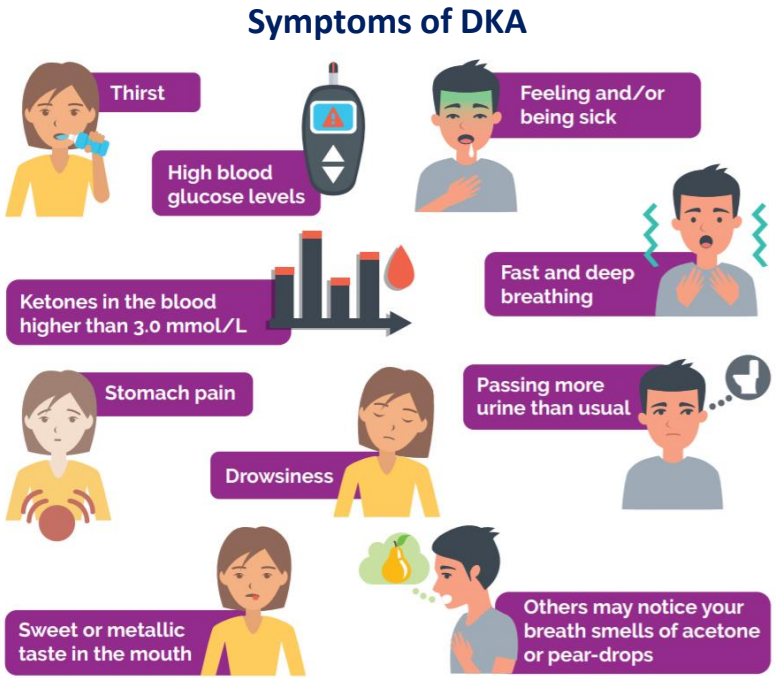
- Low insulin needs
- Not on optimal insulin dose, or recent issues with non-compliance or recurrent errors with insulin dosing
- Increased insulin requirements due to acute medical illness or surgery
- Restricts calories or carbohydrates, has a ketogenic diet or chronically under-doses insulin
- Recent or recurrent history of DKA
- Elevated ketone levels
- Unable or unwilling to monitor ketones
- Excessive alcohol consumption or illicit drug use
- Persistent eGFR ≤45 ml/min/1.73 m^2
- BMI <27 kg/m^2
- Is pregnant or breastfeeding

BMI, body mass index; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; SGLT, sodium-glucose co-transporter

1. AstraZeneca UK Ltd. Dapagliflozin summary of product characteristics. [Cited August 2019] Available from: https://www.medicines.org.uk/emc/product/2865/smpc;
2. Sanofi-Aventis groupe S.A. Sotagliflozin summary of product characteristics. [Cited August 2019] Available from: https://www.ema.europa.eu/en/documents/product-information/zynquista-epar-product-information_en.pdf

Identifying the symptoms of DKA quickly is vital

- A severe lack of insulin means the body cannot use glucose for energy, and the body starts to break down other body tissue as an alternative energy source[1]
- Ketones are the by-product of this process[1]
- If ketones build up, they cause the body to become acidic – hence the name ‘acidosis’[1]



DKA, diabetic ketoacidosis

1. Diabetes UK. Diabetes ketoacidosis (DKA). [Cited August 2019] Available from: https://www.diabetes.org.uk/Guide-to-diabetes/Complications/Diabetic_Ketoacidosis

Risk factors for DKA associated with SGLT inhibitor therapy[1]

Minimal/low

- Low BMI (<25 kg/m^2)
- Inconsistent caloric intake
- Moderate alcohol use*
- Female sex

Low/moderate

- Vigorous or prolonged exercise
- Reduced prandial insulin dose by more than 10–20%
- Travel with disruption in usual schedule/insulin regimen
- Insulin pump use

Moderate/high

- Reduced basal insulin by more than 10–20%
- Insulin pump or infusion site failure
- Reduced or inconsistent carbohydrate intake
- Excessive alcohol use
- Use of illicit drugs
- Volume depletion/dehydration
- Acute illness of any sort (viral or bacterial)

*If ketone levels increase from baseline. BMI, body mass index; DKA, diabetic ketoacidosis; SGLT, sodium-glucose co-transporter

1. Danne T, et al. *Diabetes Care* 2019;42:1147–1154.

Safety of SGLT inhibitor adjunct therapy in type 1 diabetes

Meta-analysis of 14 randomized controlled trials of SGLT inhibitors[1]
(sotagliflozin, dapagliflozin, canagliflozin, empagliflozin)
as adjunct therapy in type 1 diabetes

		Odds ratio[a]	
DKA (11 studies)		3.38[b]	CI: 1.74, 6.56
Genital tract infection (10 studies)		3.44[b]	CI: 2.34, 5.07
Urinary tract infection (8 studies)		0.97[c]	CI: 0.65, 1.46
Severe hypoglycaemia (11 studies)		0.96[c]	CI: 0.70, 1.34

[a]An odds ratio >1 favours placebo, whereas an odds ratio <1 favours the SGLT inhibitor; [b]Statistically significant increase; [c]No significant increase
CI, confidence interval; DKA, diabetic ketoacidosis; SGLT, sodium-glucose co-transporter

1. Yamada T, et al. *Diabetes Obes Metab.* 2018;20:1755–1761.

If patients feel unwell, they should stop taking the SGLT inhibitor[1]

Feel unwell?
Includes colds, upset stomachs and other minor complaints

STOP taking the SGLT inhibitor

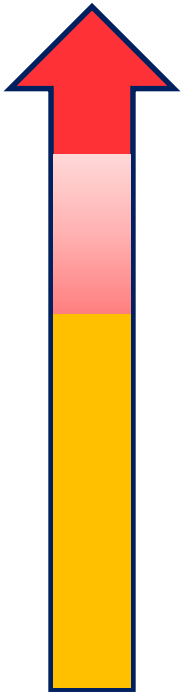
Check ketones, ***whatever*** the glucose level

SGLT, sodium-glucose co-transporter

1. Llano A, et al. *Pract Diab.* 2019;36:91–96.

Early recognition and management of DKA is critical

Actions to take in case of elevated ketones[1-3]



If blood ketone levels are >3.0 mmol/L (urine ketone = large to very large +++/++++), the patient should go to the emergency department and stop taking the SGLT inhibitor

If blood ketone levels are >1.5–3.0 mmol/L (urine ketone = moderate ++):

- Follow treatment recommendations as below
- Seek immediate medical advice and stop taking the SGLT inhibitor

If blood ketone levels are 0.6–1.5 mmol/L (urine ketone = trace or small +), treat as follows or per clinician instructions:

- May need to take extra insulin and drink water
- Consider taking extra carbohydrates if glucose levels are normal or low
- Check blood glucose frequently to avoid hyperglycaemia and hypoglycaemia
- Check blood/urine ketones (every 2 hours) until resolution
- Seek medical advice and stop taking the SGLT inhibitor if levels persist and symptoms present

DKA, diabetic ketoacidosis; SGLT, sodium-glucose co-transporter

1. Danne T, et al. *Diabetes Care* 2019;42:1147–1154; 2. AstraZeneca UK Ltd. Dapagliflozin summary of product characteristics. [Cited August 2019] Available from: https://www.medicines.org.uk/emc/product/2865/smpc; 3. Sanofi-Aventis groupe S.A. Sotagliflozin summary of product characteristics. [Cited August 2019] Available from: https://www.ema.europa.eu/en/documents/product-information/zynquista-epar-product-information_en.pdf

Patient education is essential[1]

Education can overcome the counterintuitive management of DKA

- Educate patients on DKA risk factors, ketone monitoring, and treatment protocols
- Especially important for patients for whom administration of both insulin and carbohydrates is counterintuitive when glucose levels are only slightly elevated

When to withhold the SGLT inhibitor

- Educate patients about situations in which they may want to withhold their SGLT inhibitor (increased physical activity, dehydration, altered dietary intake, alcohol consumption)
- Empower patients to decide whether or not to stop their SGLT inhibitor
- Stopping an SGLT inhibitor for a day, if in doubt, is prudent and should not cause significant metabolic issues

Educational reminders

- All patients treated with SGLT inhibitor therapy should be provided with educational materials that can serve as reminders regarding risk factors and provide ‘quick reference’ resources for treatment

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1. Danne T, et al. *Diabetes Care* 2019;42:1147–1154.

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