PART 2 | WHAT DO YOU KNOW ABOUT?

Sodium–glucose cotransporter 2 (SGLT2) inhibitors

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SGLT2 inhibitors, also called gliflozins, are a class of medications that inhibit renal tubular reabsorption of glucose. They are approved for use to lower blood sugar in adults with type 2 diabetes. Apart from blood sugar control, gliflozins have been shown to provide significant cardiovascular benefit in T2DM patients.

Canagliglozin, empagliflozin and dapagliflozin have been approved and many others are currently under development.

With the increasing evidences about their proved beneficial effect in diabetic chronic kidney disease and heart failure patients, many societies recommended the addition of gliflozins to the therapeutic plans. Figure 1 shows the site of action of SGLT 2 inhibitors.

So, let us find why these medications are of increasing interests in modern medical practice.

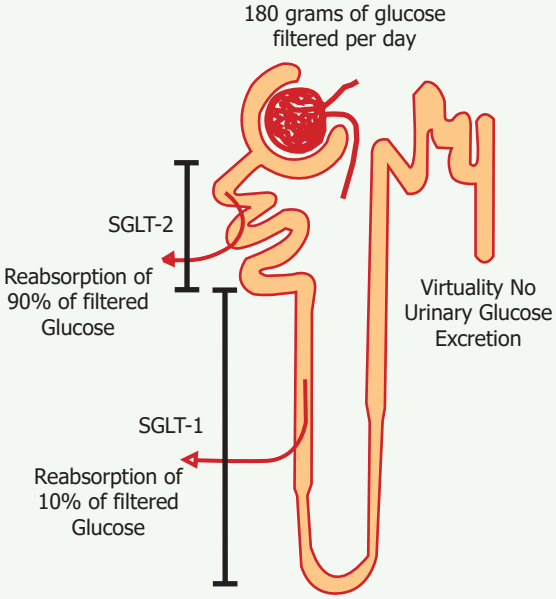

Figure 1: The site where SGLT-1 and 2 exert therir action

Choose the best appropriate answer for each statement:

1. Physiological bases of SGL2 Inhibition:

(a) All SGLT1 and 2 exclusively present in the distal part of the nephron.

(b) SGLT1 and 2 also present in the Intestine.

(c) SGLT2 is a high capacity low affinity transporter in contrast to SGLT1.

(d) SGLT2 missense mutation leads to glucose-galactose malabsorption.

2. The following is not true about the effect of SGLT2 inhibitors on glycaemic control:

(a) Modest reduction in HbA1c (0.7%).

(b) Decrease insulin level.

(c) Neutral impact on hypoglycaemia.

(d) Decrease insulin sensitivityy.

3. SGLT2 inhibitors are associated with a reduction in blood pressure of approximately:

(a) 1% to 3%.

(b) 3% to 5%.

(c) 5% to 7%.

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(d) 7% to 9%.

4. Which of the following is incorrect?

(a) In health, up to 180 gm of glucose is filtered through the glomerulus and is completely reabsorbed.

(b) SGLT2 is high capacity, low affinity transporter & reabsorbs up to 90% of glucose, rest 10% is by SGLT1.

(c) SGLT2 is down-regulated in diabetics.

(d) The action of SGLT2 inhibitors depends upon renal functions.

5. What is true about SGLT2I and weight loss?

(a) Osmotic diuresis and loss of body water - is the probable mechanism in early stage.

(b) Decrease body fat is the probable mechanism in the late stage .

(c) There is no weight loss associated with SGLT2i.

(d) Both A & B.

6. The following is true about SGLT2I except:

(a) They increase Na delivery to macula densa and activate tubulo-glomerular feedback.

(b) They do not cause reflex tachycardia despite haemodynamic effects.

(c) They decrease Sympathetic Nervous System activation.

(d) The probable positive CV impact is due to hypoglycemic effect.

7. SGLT2I approved to be initiated in the following situation:

(a) Type 2 DM as a first line drug.

(b) Type 2 DM with established CV disease.

(c) Type 1 DM and Type 2 DM with established CV disease.

(d) Protection of the myocardium in Acute Coronary syndrome .

8. The lowest acceptable GFR to initiate SGLT2I is:

(a) 30 ml/mi/1.73 m^2.

(b) 35 ml/mi/1.73 m^2.

(c) 40 ml/mi/1.73 m^2.

(d) 45 ml/mi/1.73 m^2.

9. Adverse events of SGLT2I:

(a) Increased risk of cancer.

(b) Euglycemic DKA.

(c) Volume depletion associated acute kidney injury.

(d) All SGLT2I reduce bone density and predispose to fracture.

10. SGLT2I and urogenital infections:

(a) Urosepsis is common.

(b) There is a significantly higher risk of UTI when compared to diabetic patients using other oral anti-diabetic agents.

(c) There is substantially higher risk of genital infections.

(d) Higher doses of empagliflozin are associated with an increased risk of urogenital infections.

Answers are on the next page

Sodium–glucose cotransporter 2 (SGLT2) inhibitors

Answers of the Questions

1. ***The correct answer is (c)***: In kidneys, SGLT2 is present in the proximal part of the tubules while SGLT1 is present more distally. SGLT1 is present in the intestine and kidneys. SGLT2 is a high capacity low affinity transporter in contrast to SGLT1. The essential nature of SGLT1 is confirmed by the rare genetic disease glucose-galactose malabsorption (GGM), which arises from missense mutations in SGLT1.

Reference: Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Sodium–glucose cotransporter inhibitors: effects on renal and intestinal glucose transport: from bench to bedside. ***Diabetes care***. 2015 Dec 1;38(12):2344-53.

Message: (***To understand the mechanism of action through the renal tubules and the possible targets of therapy***)

2. ***The correct answer is (d)***: *SGLT2I produce modest reduction of HbAIc and a neutral effect on hypoglycaemia. With the improved glycaemic control and better response and sensitivity to insulin, the insulin level will be less than the usual phenotype of type 2 DM.*

Reference: Sang Soo Kim, Jong Ho Kim, Su Mi Lee, Il Young Kim and Sang Heon Song (October 24th 2018). New Tubulocentric Insights for Diabetic Nephropathy: From Pathophysiology to Treatment, Advances in Nephropathy, Thomas Rath, IntechOpen.

Message: (***In a milieu of type 2 DM, insulin resistance is attributed to cardiovascular complications. Improving insulin sensitivity is another target beyond glucose lowering.***)

3. ***The correct answer is (b)***: SGLT2 inhibitors consistently reduce BP, an effect that is commonly explained by their diuretic/natriuretic effects and perhaps by other mechanisms, such as a reduction of arterial stiffness. This may be an additive effect to ACEi/ARBS used to control blood pressure inpatients with type 2 DM.

Reference: : Scheen AJ, Delanaye P. Effects of reducing blood pressure on renal outcomes in patients with type 2 diabetes: Focus on SGLT2 inhibitors and EMPA-REG OUTCOME. ***Diabetes Metab***. 2017;43(2):99–109.

Message: (**Control of blood pressure is another important target to be achieved when managing patients with type 2 DM**)

4. ***The correct answer is (c)***: The normal physiology of glucose metabolism involves filtration of up to 180 gm of glucose is through the glomerulus with complete reabsorption. SGLT2 is high capacity, low affinity transporter & reabsorbs up to 90% of glucose, rest 10% is by SGLT1. There is 4-fold up-regulation of SGLT2 expression in diabetes. Given the mode of action, the glucose-lowering efficacy of SGLT2 inhibitors depends on renal function and on plasma glucose levels.

Reference: Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Sodium–glucose cotransporter inhibitors: effects on renal and intestinal glucose transport: from bench to bedside. ***Diabetes care***. 2015 Dec 1;38(12):2344-53.

Message: (**To know the renal contribution to glucose metabolism and control.**)

5. ***The correct answer is (d)***: Early loss is due to osmotic diuresis while later it is due to decreased body fat due to negative glucose balance secondary to increased urinary glucose excretion. The ability to reduce body weight is consistently observed in individuals taking SGLT2 inhibitors, but this weight loss is moderate due to counter-regulatory mechanisms striving to maintain body weight. This has prompted exploration of SGLT2 inhibitors in combination with other agents acting via decreased food intake to be a possible therapeutic intervention for obesity with or without type 2 DM.

Reference: Pereira MJ, Eriksson JW. Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity. ***Drugs***. 2019;79(3):219–230. doi:10.1007/s40265-019-1057-0.

Message: (**Any medication that promotes weight loss is beneficial for reducing metabolic complications in type 2 DM.**)

6. ***The correct answer is (d)***: As they inhibit SGLT2 in the proximal part of the nephron, the gliflozins increase Na delivery to macula densa and activate the tubule-glomerular feedback. In spite of the haemodynamic effects they do not cause reflex tachycardia. In addition, they decrease Sympathetic Nervous System activation. Other oral therapies for diabetes produce similar effects on A1C but they didn't show similar renal and cardiovascular outcomes, so the protective effect of SGLT2I is not merely dependent on hypoglycemia.

Reference: Rocha NA, McCullough PA. Cardiovascular outcomes in diabetic kidney disease: insights from recent clinical trials. ***Kidney Int Suppl*** 2011. 2018;8(1):8–17.

Message: (**The cardiovascular protective effects of SGLT2I are beyond glucose lowering**)

7. ***The correct answer is (b)***: It is not yet formally approved for type 1 DM. If to be given as adjunctive therapy to insulin, the risk of possible euglycaemic ketosis should be balanced against the potential glycaemic control. It is approved as add-on after metformin for T2DM according to the recent ADA recommendations. It may reduce cardiovascular risk but still can't be used in the context of acute coronary syndrome.

Reference: Taylor SI, Blau JE, Rother KI, Beitelshees AL. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: balancing benefits and risks. ***Lancet Diabetes Endocrinol***. 2019;7(12):949–958.

Rocha NA, McCullough PA. Cardiovascular outcomes in diabetic kidney disease: insights from recent clinical trials. ***Kidney Int Suppl*** 2011. 2018;8(1):8–17.

Message: (**The established indications of gliflozins is type 2 DM, but they have many potential indications for different patients' settings.**)

8. ***The correct answer is (a)***: The American Diabetes Association has updated its diabetes standards of care to incorporate results from the CREDENCE trial, published in the New England Journal of Medicine. In the placebo-controlled trial, the sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin was associated with reduced risk for cardiovascular events and renal failure in patients with type 2 diabetes and chronic kidney disease (CKD). For patients with type 2 diabetes and diabetic kidney disease, clinicians should consider using an SGLT2 inhibitor when the eGFR is at or above 30, especially with albuminuria above 300 mg/g, to lower renal and CV risk.

Reference: Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. ***N Engl J Med***. 2019;380(24):2295–23068.

Message: (**SGLT2I can be used at low GFR (30 ml/min) with a renal protective effect**)

9. ***The correct answer is (b)***: There was No increased risk of cancer in most trials. Euglycemic DKA may occur but mainly when there is a predisposing factor to DKA like infection. No increased rates of AKI were reported in the major RCTs. Caution is advised when volume depletion conditions or drugs affecting renal hemodynamics coexist. Based on current evidence, only canagliflozin may be associated with decreased bone mineral density in the hip and increased fracture rates.

Reference: Filippas-Ntekouan S, Filippatos TD, Elisaf MS. SGLT2 inhibitors: are they safe? ***Postgrad Med***. 2018;130(1):72–82. doi:10.1080/00325481.2018.1394152.

Message: (**SGLT2Is are relatively safe**)

10. ***The correct answer is (c)***: There is no significant difference in the risk of UTI with SGLT-2 inhibitors compared to placebo or active comparator. UTIs complicated by urosepsis rarely occur. The risk of genital tract infections was substantially higher in patients taking SGLT-2 inhibitors compared to placebo. Higher doses of dapaglifozin are associated with an increased risk.

Reference: Puckrin R, Saltiel MP, Reynier P, Azoulay L, Yu OHY, Filion KB. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. ***Acta Diabetol***. 2018;55(5):503–514.

Message: (**SGLT2Is don't increase UTI but more genital infections**)