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BMH Medical Journal 2015;2(4):97-101 **Review Article**

SGLT 2 Inhibitors: A New Therapeutic Target And Its Role In Current Clinical Practice

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Introduction

Diabetes, one of the major life style diseases, is associated with high morbidity and mortality owing to its microvascular and macrovascular complications. The chance of development of various complications can be effectively prevented by tight glycemic control. We have various groups of drugs like Biguanides, Sulfonyl ureas, Glitazones, Alpha-glucosidase inhibitors, Incretin based therapy, Insulin and Insulin analogues in the armamentarium to treat diabetes. But still, the number of patients attaining glycemic targets are relatively low and various adverse effect limit the use of some of these drugs, especially in special groups. Hence there is ongoing research to develop newer and newer drugs which provide sustained blood glucose reduction with minimal adverse effects. SGLT-2 inhibitors are a new group of drugs recently approved by FDA to treat Diabetes. In this review we discuss about mechanism of action, various adverse effects and the clinical role of various SGLT-2 Inhibitors.

Renal Handling of Sodium and mechanism of action of SGLT 2 Inhibitors in Diabetes

The dietary glucose is filtered at the glomerulus and enters the tubular lumen from where it is almost completely reabsorbed, in the normal individual making urine free of glucose [1]. About 90% of filtered glucose is reabsorbed in the segment S1/ S2 of proximal convoluted tubules with the help of SGLT-2 (Sodium Glucose Co- transporter -2) and the remaining 10% from the S3 segment of proximal convoluted tubules with the help of SGLT-1. SGLT2 is a low-affinity, high-capacity glucose transporter, where as SGLT1 is a high-affinity, low-capacity glucose/galactose transporter [2] (see **Table 1**). But when the blood sugar value exceeds the normal renal threshold (i.e. blood sugar value of 180-200 mg/dl) glucose starts appearing in urine. Even in diabetic patients with severe hyperglycemia, renal reabsorption of glucose continues, contributing to the severity of hyperglycemia. In Diabetic patients there is also up regulation of SGLT-2 mediated glucose reabsorption, further aggravating hyperglycemia.

Table 1: Different types of SGLT receptors and their functions

Type of SGLT	Major sites	Functions : Transport of
SGLT 1	Small intestine, Heart, Trachea, Kidney(S3)	Na, Glucose Galactose
SGLT 2	Kidney(S1, S2)	Na, Glucose
SGLT 3	Small intestine, Uterus Lung, Thyroid, Testis	Na
SGLT 4	Small intestine, Kidney, Liver, Stomach, Lung	Glucose, Mannose
SGLT 5	Kidney	Unknown
SGLT 6	Spinal cord, Kidney, Brain, Small intestine	Myoinositol, Glucose

Blocking SGLT-2 in the proximal convoluted tubules leads to decreased reabsorption of filtered glucose from the tubular lumen and thereby increased exertion of glucose in the urine. So SGLT-2 inhibitors help to achieve better glycemic control and reduction in the amount of already ingested calories [3]. But inhibition of SGLT-2 mediated glucose reabsorption can lead to compensatory up regulation of SGLT-1 mediated glucose reabsorption, to some extent, in the S3 segment.

SGLT 2 inhibitors

Canagliflozin,dapagliflozin and empigliflozin are the currently available FDA approved SGLT2 inhibitors.

Canaglifozin

Canaglifozin was the first SGLT2 inhibitor to be approved by FDA in 2013. It can be used alone or in combination with other antidiabetic drugs. Recommended starting dose is 100 mg once daily and could be given to a maximum dose of 300 mg/day. It can be used with other antidiabetic drugs and also with insulin. It has insulin independent action as described above by increasing glucosuria by inhibiting SGLT2 in the renal tubules. It also produced decrease in blood pressure and also body weight. It can be used safely in mild to moderate hepatic and renal failure patients. When Canaglifozin is taken orally it gets rapidly absorbed from gastrointestinal tract in a dose dependent manner . Mean oral bioavailability is approximately 65%. Median $t_{1/2}$ is 1-2 hours and steady state concentration is achieved after 4 to 5 days of daily intake of 100 mg and 300 mg. When used along with UGT enzyme inducers like rifampin the dosage should be increased. Canagliflozin when used along with digoxin it's toxicity can be precipitated. In pregnancy it is not safe as there are no adequate data to suggest its safety. Like wise in nursing mothers also it is not advised. In geriatric patients side effects due to volume depletion are more [4]. The CANagliflozin Treatment And Trial Analysis (CANTATA Trials) [5] evaluated Canagliflozin as monotherapy or as an add-on therapy to metformin, metformin and sulphonylurea and metformin and pioglitazone and it was found that canagliflozin produced better improvement in FPG, HbA1c and systolic blood pressure and also caused weight reduction. The CANTATA trials have concluded that Canagliflozin could be taken as an initial drug for T2DM patients whose glycemic control is not achieved with diet and exercise; and also as an effective alternative to sulphonylurea, sitagliptin or pioglitazone in dual therapy with metformin.

Dapagliflozin

Dapagliflozin has similar effects to Canagliflozin. It selectively inhibits sodium-glucose cotransporter 2 (SGLT-2) in the proximal renal tubules, reduces absorption of filtered glucose from the tubular lumen and increases urinary excretion of glucose. Tmax is 2 hours. It is 90% protein bound and excreted primarily via urine (75%) and feces(21%). The side effects are similar to Canagliflozin. It is contraindicated in severe renal and hepatic failure. It is also contraindicated in pregnant and nursing mothers [6].

The dosage and important effects of other SGLT 2 inhibitors are given in **Table 2**.

Table 2: SGLT- 2 Inhibitors: dose and effect on HbA1c and body weight

Drug	Dose (mg/day)	HbA1c reduction (%)		Bodyweight
Dapagliflozin	2.5-10	0.58-0.97		3.0 Kg
Canagliflozin	50-300mg/day	0.7-1.0		2.3-2.4 Kg
Empagliflozin	1-50 mg/d	0.72		2.9 Kg
Ipragliflozin	12.5-100Mg/day	0.8		2.0 Kg
LX4211*	150-300	1.25		
PF-04971729	1-25mg/day	0.83		2.9 Kg
Tofogliflozin	20			
Luseogliflozin	2.5-5			
Ertugliflozin	5-10			
Vemgliflozin				

*Block both SGLT 1 and SGLT 2

Benefits of SGLT 2 inhibitors

The major therapeutic benefits of SGLT 2 inhibitors are: [7,8,9]

1. Decreases blood sugar level by reducing glucose reabsorption from the kidneys there by increasing urinary loss of calories.
2. Reduces body weight, hence a better option for obese diabetics and also to combine with other anti-diabetic drugs, which causes weight gain.
3. Mechanism of action is independent of insulin secretion or insulin action. So it is effective in both severely insulinopenic and severely insulin resistant diabetics.
4. Risk of hypoglycemia is less.
5. Can be combined with other anti-diabetic drugs.
6. Reduces both systolic and diastolic blood pressure

Adverse effects of SGLT 2 inhibitors

These group of drugs cause significant glucosuria. The increased amount of glucose in urine can cause increased risk of genital and mycotic infections. They can also cause dehydration as glucose is an osmotic diuretic. Due to the same reasons these group of drugs can cause hypotension especially in elderly subjects. But the extent of osmotic load is relatively modest especially in case of canagliflozin not leading to marked changes in plasma volume and urinary output. They can also be

used safely in mild to moderate renal and hepatic failure [10].

Use SGLT 2 inhibitors cautiously in:

1. Elderly patients because of tendency to dehydration and urinary and genital infections.
2. Patients with recurrent urinary tract or genital infections.
3. Patients with reduced renal function because of reduced efficacy.

Role of SGLT 2 inhibitors in current clinical practice

In Jan 2015 issue of Diabetes Care, ADA as well as EASD has given an update of 2012 ADA guidelines regarding usage of SGLT-2 inhibitors. Metformin still remains drug of choice for mono therapy in type 2 diabetes mellitus, but SGLT2 inhibitors can be given as a second or third line drug. SGLT-2 inhibitors can be added to metformin or sulfonylurea with metformin if glycemic goals are not met. Trials have also shown that a combination of SGLT-2 inhibitors and dipeptidyl peptidase inhibitors also produces a good reduction in HbA1c. There is also propensity to use SGLT-2 inhibitors along with insulin in both type 1 and type 2 diabetes.

Conclusion

All the data presented on SGLT-2 inhibition are very encouraging, but there is still reason for caution, because these drugs are very new and the duration of studies available at present are so limited. The balance of benefits versus risks is still not well understood and it will take time to fully evaluate this issue. But still these group of drugs open up new avenues for better glycemic targets in diabetes management.

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