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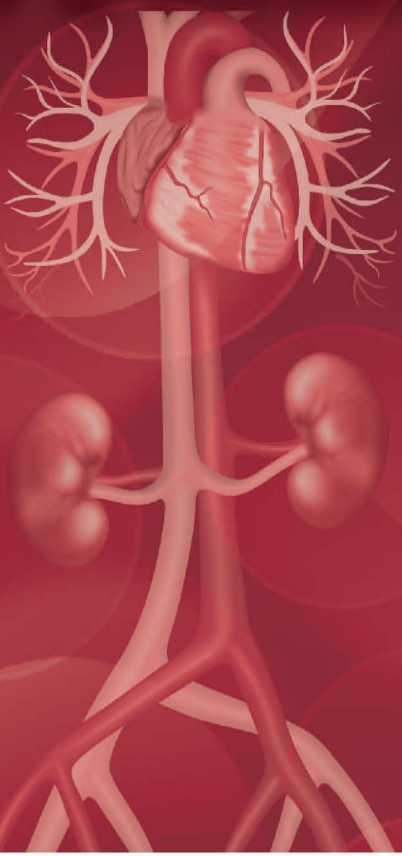
Novel Insights on SGLT-2 Inhibitors



Authors
Rajeev Chawla
Shalini Jaggi

Foreword
Paresh Dandona

JAYPEE

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3

CHAPTER

Beyond Glycosuria: Exploring the Intrarenal Effects of SGLT-2 Inhibition in Diabetes

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INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a novel class of oral antidiabetic drugs which produce renal glycosuria by inhibiting renal tubular glucose reabsorption via blocking SGLT-2 located at the luminal membrane of tubular cells of the proximal convoluted tubule. SGLT-2 inhibitors produce nephroprotection by not only improving glycemic control but also through glucose-independent direct renal effects and blood pressure-lowering. Glomerular hyperfiltration is likely to worsen diabetic nephropathy (DN). Glomerular hyperfiltration in diabetes occurs because of overactivation of renal tubular factors, including SGLT-2 and renin–angiotensin–aldosterone system. SGLT-2 inhibitors lead to reduction in hyperfiltration by inhibiting sodium reabsorption in the proximal tubule through tubuloglomerular feedback, causing afferent arteriole vasoconstriction and decrease fibrotic response of proximal tubular cells and inflammation. SGLT-2 inhibitors, however, do not produce significant glycemic reduction in patients with impaired renal function, given their mode of action. SGLT-2 inhibitors are in advantageous position as these function independent of β-cells, insulin secretion, and action. Therefore, their efficacy is maintained despite of progressive β-cell failure in type 2 diabetes mellitus (T2DM). They are very well tolerated, and carry a low risk of hypoglycemia.

The efficacy, safety, and mechanism of action of SGLT-2 inhibitors, in patients with normal and impaired renal function as mild, moderate, or severe renal impairment, is discussed. Beneficial effects of SGLT-2 inhibitors on renal function especially on albuminuria, hyperfiltration, and diabetic tubulointerstitial fibrosis are also discussed here.

SGLT-MEDIATED GLUCOSE TRANSPORTATION

Although glucose is the main fuel and source of energy but sustained hyperglycemia is driver of diabetic complications. Glucose is retained through number of biochemical processes and complicated transport systems. Kidneys try to preserve glucose via tubular glucose reabsorption through sodium-glucose cotransporters (SGLTs), secondary active cotransporters, and facilitative glucose transporters (GLUTs). SGLT-1 and SGLT-2, which are located in the brush border of the tubular cells at the proximal tubule, are members of the *SLC5* gene family and are secondary active SGLTs. SGLT-2 cotransporters have low affinity but very high capacity for glucose transportation and 1:1 sodium-glucose coupling and reabsorb approximately 80–90% of the filtered glucose. SGLT-1 transporters are located in the straight (S3) segment of the proximal tubule and have high affinity/low capacity for glucose and 2:1 sodium-glucose coupling and reabsorb the remaining 10–20% of glucose that "escapes" SGLT-2 reabsorption. SGLT-1 transporters are mainly expressed in the enterocytes of the small intestine apart from the kidney and facilitate both galactose and glucose absorption.

FACILITATIVE GLUCOSE TRANSPORTERS

Glucose transporter 1 and GLUT2 are part of GLUT (SLC2A) protein family and function as facilitative glucose transporters. GLUT1 facilitates glucose diffusion from the tubular cells intracellular space to the renal interstitial through the basolateral membrane at the proximal straight tubule (S3 segment) and GLUT2 at proximal convoluted (S1/2 segment) tubule.

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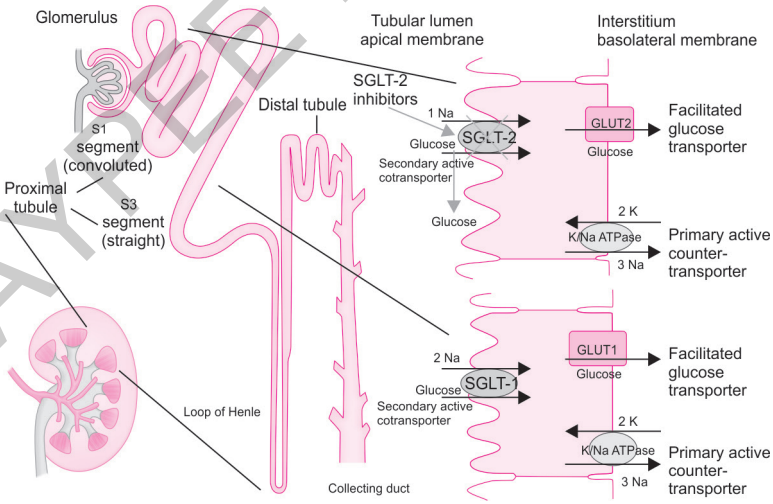
MECHANISM OF TUBULAR GLUCOSE REABSORPTION (FIG. 1)

Sodium-potassium adenosine triphosphate (ATP)ase is located in the basolateral membrane of proximal tubular cells (PTCs) and is an active transporter and constitutes the source of energy for the glucose reabsorption transport system. Main fuel for the transportation of sodium ions to the kidney interstitium through the basolateral membrane of tubular cells comes from ATP hydrolysis. A negative electrical potential is created due to reduction of the intracellular sodium concentration which then induces sodium diffusion from the tubular lumen to the tubular intracellular space through SGLT cotransporters simultaneously driving glucose against its gradient, from the lumen into the tubular cells. Glucose diffuses to the kidney interstitium through GLUTs at the basolateral membrane after entering the tubular cells.

The sodium-potassium ATPase pump a primary active counter-transporter, is located at the tubular cells of the S1 and S3 segment of the proximal convoluted tubule. It exports sodium to the interstitium and imports potassium. Required energy for this function comes



(GLUT2: glucose transporter 2; SGLT-2: sodium-glucose cotransporter-2)

FIG. 1: A model for renal glucose reabsorption.

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from ATP-ADP transformation while sodium gradient needed for the operation comes from this pump. Sodium transportation happens along its gradient while glucose moves against its electrochemical gradient. GLUTs located at the basolateral membrane of the tubular cells facilitate passive glucose diffusion intracellularly to the interstitium. Concerning SGLTs, cotransporters on the brush border of tubular cells, SGLT-2 is located at the S1 segment and has 1:1 sodium to glucose stoichiometry while SGLT-1 is found at the S3 segment and has 2:1 stoichiometry.

PHYSIOLOGY OF GLUCOSE REABSORPTION

Kidneys filter 160–180 g of glucose daily in healthy individuals which is then reabsorbed within the proximal tubules leading to glucose conservation. Glucose filtered by the glomerular capillary membrane passes into the tubular lumen. Under normoglycemic conditions, the blood glucose concentration is 90–100 mg/dL and glomerular filtration rate (GFR) is about 180 per day. Approximately 162–180 g of glucose filters from the Bowman's capsule into the tubular lumen which is reabsorbed by the tubular GLUTs; hence, in a nondiabetic person, glucose is not excreted in the urine. With increasing hyperglycemia, tubular glucose reabsorption increases linearly till SGLTs reach their maximum transport capacity leading to saturation of glucose transport system. Transport maximum (TmG) corresponds with a blood glucose level of approximately 300 mg/dL, referred as the threshold for glucose (300 mg/dL is the quotient of TmG 375 mg/min and GFR 125 mL/min) and for the glucose tubular transport system in adults, it is about 375 mg/min. Once glucose level is above the level of TmG, excess glucose filtered is not reabsorbed and passes into urine.

ALTERATIONS OF RENAL GLUCOSE REABSORPTION IN DIABETES

Above the saturation threshold, with increasing plasma glucose, urinary glucose excretion increases in a linear fashion. The reabsorption curve gets shifted to the right in T2DM. TmG is 20% elevated in diabetics compared with healthy adults. In hyperglycemic states, glucose reabsorption is enhanced and hyperglycemia is

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further exacerbated because the mechanism of energy retention through glucose reabsorption becomes maladaptive in diabetic patients.

GENETIC DEFECTS IN RENAL GLUCOSE TRANSPORT

Renal glycosuria has been shown to occur due to specific mutations in the *SGLT* genes. Glucose-galactose malabsorption (GGM), a rare disorder due to mutations in the SGLT-1, leads to malabsorption of these sugars because of failure of the gastrointestinal epithelial cells to accumulate them across the brush border membrane. This manifests as diarrhea and dehydration in the neonatal period which improves by omitting glucose and galactose (also transported by SGLT-1) from the diet. These subjects have either mild or no glucosuria owing to the minor role of SGLT-1 in renal glucose reabsorption.

Familial renal glucosuria (FRG), a rare autosomal recessive disorder, results due to mutations in the *SLC5A2* gene that code for SGLT-2. Heterozygous FRG is a benign condition and does not have any renal tubular dysfunction but leads to glucosuria of 0–10 g/day even at normal plasma glucose concentrations. Homozygous FRG, with glucosuria of 200 g/day is rarely seen though this condition is largely asymptomatic. Encouraging initial studies on SGLT-2 inhibitors along with benign features of FRG stimulated further research into SGLT-2 inhibition as a therapeutic intervention for T2DM.

SGLT-2 INHIBITORS OFFER RENOPROTECTION

Sodium-glucose cotransporter-2 inhibitors not only improve glycemia but offer renoprotection through nonglycemic benefits in type 2 diabetics. Various studies have shown that glucose entry into tubular cells results into tubulointerstitial fibrosis, involving both PTCs, basement membrane alterations, and interstitial fibrosis leading to development of diabetic nephropathy. More evidence is emerging that SGLT-2 inhibitors, having beneficial effects on the afferent renal arteriole (constriction of the afferent arteriole), once combined with renin–angiotensin–aldosterone system (RAAS)

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inhibition which induces changes in R_E (efferent arteriole vasodilatation), may have cumulative renoprotective effect.

CONCLUSION

Kidneys till date have been victim of hyperglycemia but presently are being used as a partner in management of T2D. SGLT-2 inhibitors, a new class of antihyperglycemic agent, induce significant glucosuria and reduce hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) levels. SGLT-2 inhibitors work independent of β-cells and do not interfere with insulin secretion and action; hence, β-cell progressive failure does not impair their efficacy. Efficacy of these agent decreases with stages of renal impairment; however, as the glucosuric effect depends on renal function. SGLT-2 inhibition results in weight and blood pressure reduction due to consistent calorie loss and osmotic diuresis as a result of glucosuria. SGLT-2 inhibitors are generally well tolerated with very low risk of hypoglycemia and the most common adverse events being urinary tract infections (UTIs) and gastrointestinal disorders(GIs) but these can be minimized by ensuring enough oral liquids intake and maintaining personal hygiene.

SUGGESTED READING

1. Abdul-Ghani M, DeFronzo R. Inhibition of renal glucose reabsorption: a novel strategy for achieving glucose control in type 2 diabetes mellitus. Endocr Pract. 2008;14:782-90.
2. Abdul-Ghani M, DeFronzo R. Lowering plasma glucose concentration by inhibiting renal sodium-glucose co-transport. J Intern Med. 2014;276:352-63.
3. Berhan A, Barker A. Sodium glucose co-transport 2 inhibitors in the treatment of type 2 diabetes mellitus: a meta-analysis of randomized double-blind controlled trials. BMC Endocr Disord. 2013;13:58.
4. DeFronzo R, Davidson J, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab. 2012;14:5-14.
5. DeFronzo R. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58:273-95.
6. Ferrannini E, Veltkamp S, Smulders R, et al. Impact of chronic kidney disease and sodium-glucose cotransporter 2 inhibition in patients with type 2 diabetes. Diabetes Care. 2013;36:1260-5.
7. Gilbert R, Cooper M. The tubulointerstitium in progressive diabetic kidney disease: more than an aftermath of glomerular injury? Kidney Int. 1999;56:1627-37.

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8. Hediger M, Rhoads D. Molecular physiology of sodium-glucose cotransporters. Physiol Rev. 1994;74:993-1026.
9. Jerums G, Premaratne E, Panagiotopoulos S, et al. The clinical significance of hyperfiltration in diabetes. Diabetologia. 2010;53:2093-104.
10. Magee G, Bilous R, Cardwell C, et al. Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis. Diabetologia. 2009;52:691-7.
11. Novikov A, Vallon V. Sodium glucose cotransporter 2 inhibition in the diabetic kidney: an update. Curr Opin Nephrol Hypertens. 2015;24:1-9.
12. Ruggenenti P, Porrini E, Gaspari F, et al. Glomerular hyperfiltration and renal disease progression in type 2 diabetes. Diabetes Care. 2012;35:2061-8.

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Novel Insights on
SGLT-2 Inhibitors

Key Features

- This book provides detailed information on the novel drug class SGLT-2 inhibitors for the treatment of diabetes
- All current evidences, studies and available data have been incorporated in the writing of this book to bring to the readers an updated overview of this novel drug class
- An in depth search of literature on all topics traces how the SGLT-2 inhibitors have evolved and are now a preferred option in management of type 2 diabetes, with promising data emerging on their use in type 1 diabetes as well
- The book has been written in simple language and a standard pattern with a crisp introduction of the topic to brief the reader on what to expect in the text, followed at the end by a short conclusion that sums up the text for quick reference of its readers
- The book is aimed at all health care practitioners, physicians and medical students/postgraduates with an avid interest in the latest advances in the evolution of this drug class for diabetes management
- Written by experts in the field of diabetes with a vast clinical experience with these agents.

Rajeev Chawla
MD FRSSDI FACP (USA) FRCP UK (Edin) FACE (USA)
Senior Consultant Diabetologist and Director
North Delhi Diabetes Centre
New Delhi, India

Shalini Jaggi
Dip Diab (UK) Dip Endo (UK) FRSSDI FRCP (London, Glas, Edin) FACE (USA)
Consultant and Head
Dr Mohans' Diabetes Specialities Centre
New Delhi, India

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ISBN 978-93-5270-680-8