Sodium Glucose Cotransporter 2 Inhibitors

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KEYWORDS

• Sodium glucose cotransporter 2 • SGLT2 • SGLT2 inhibitors • Type 2 diabetes
• Antihyperglycemic agents

KEY POINTS

- Sodium glucose cotransporter 2 (SGLT2) inhibition offers a novel mechanism to mitigate hyperglycemia in patients with diabetes.
- SGLT2 inhibitors are generally associated with a reduction in hemoglobin A1c of between 0.5% and 1%.
- The mechanism of action and efficacy of SGLT2 inhibitors are not linked to insulin and are associated with an exceedingly low incidence of hypoglycemia when used independently of exogenous insulin or secretagogues.
- SGLT2 inhibitors are associated with an increased incidence of urinary tract and genital infections but these infections are typically mild, responsive to treatment, and are not use limiting.

INTRODUCTION

For much of the history of modern medicine the kidney has been thought of as primarily an organ of elimination of waste materials and a regulator of ion balance.[1] The impact of the kidney on glucose homeostasis was for the most part unrecognized until it was incorrectly implicated as the structural cause of diabetes in the late 1800s. It is now known that the kidney plays other roles and is involved intimately in glucose metabolism and homeostasis. Advances in the recognition of the role that the kidney plays in glucose homeostasis and metabolism has over the past few decades fueled an interest in modulation of these systems for therapeutic reasons. One area of particular interest has been the sodium glucose cotransporters (SGLTs). At present, several medications for the management of type 2 diabetes are on the market that inhibit SGLTs (specifically SGLT2).

This article reviews the role of the kidney in glucose regulation in nondiabetic and diabetic patients. It also discusses the therapeutic modulation of SGLT for therapeutic

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reasons and specifically review the development of the SGLT2 inhibitors. Individual SGLT2 inhibitors, their use in patients with renal disease, and drug-drug interactions with these agents are discussed, as well as the overall potential benefits and adverse effects.

THE KIDNEY AND GLUCOSE REGULATION

The kidney has not always been thought of as one of the major organs responsible for glucose homeostasis. However, the kidney plays a major role in glucose metabolism and homeostasis via at least 3 processes: (1) gluconeogenesis, (2) glucose use, and (3) glomerular filtration and reabsorption of glucose in the proximal convoluted tubules.[2] In addition, there are significant perturbations in each of these key processes in patients who have diabetes.

Renal Gluconeogenesis

The endogenous production and release of glucose into the circulation occurs either by gluconeogenesis (GNG) or glycogenolysis. In individuals who have fasted for greater than 14 hours, about half of the endogenously produced glucose released into the circulation comes from the production of glucose by the kidney or liver (GNG) and about half comes from the breakdown of glycogen stores in the liver (glycogenolysis).[2,3] It has also been suggested that the small intestines may play role in GNG in some species.[4] In humans, the liver and the kidney are the only organs that possess sufficient quantities of glucose-6-phosphatase and other enzymes needed to drive gluconeogenesis. The kidney is important in this regard because renal glucose production accounts for about 20% to 25% of glucose released into the circulation after a fast of 12 to 16 hours. The kidney is responsible for one-fifth of overall endogenous glucose release and is responsible for approximately 40% of glucose released specifically by gluconeogenesis.[2,3]

Endogenous glucose liberation is reduced by about 60% overall in the postprandial state.[5] Hepatic glycogenolysis is essentially extinguished several hours after a meal and hepatic gluconeogenesis reduced by about 80%. In the postprandial state, renal gluconeogenesis is increased by 100% and accounts for 60% of endogenous glucose release. One theory suggests that this increase in postprandial renal gluconeogenesis is directed toward building hepatic glycogen stores.

The role of gluconeogenesis as a factor in worsening hyperglycemia in patients with both types 1 and 2 diabetes has been documented.[3] Significant increases in renal gluconeogenesis have been shown in animal diabetes models and in human studies. Studies in patients with type 1 and type 2 diabetes have shown that renal glucose release increases in about the same proportion as hepatic glucose production does in these patients. In patients with type 2 diabetes an increase (compared with people with normal glucose tolerance) in both fasting and postprandial gluconeogenesis has been shown.[2]

Renal Glucose Use

The kidneys have an important role in glucose use. In the fasting state the kidneys use approximately 10% of all the glucose used by the body for energy. The amount of glucose used increases significantly (approximately 3-fold) in the fed state but proportionally is still about 10% of all of the glucose used.[5] Patients with type 2 diabetes have significantly increased renal glucose uptake compared with nondiabetic individuals in both the fasting and postprandial states. Glucose use is approximately 3-fold higher in the fasting state and 2-fold higher in the postprandial state in patients with type 2 diabetes versus nondiabetic individuals.[5]