SGLT2 Inhibition for the Prevention and Treatment of Diabetic Kidney Disease: A Review

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Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease in the United States and the world alike, and there is a great unmet need for treatments to reduce DKD development and progression. Inhibition of sodium/glucose co-transporter 2 (SGLT2) in the proximal tubule of the kidney has emerged as an effective antihyperglycemic treatment, leading to regulatory approval of several first-generation SGLT2 inhibitors for the treatment of type 2 diabetes. In follow-on clinical trials for the cardiovascular safety of the SGLT2 inhibitors, secondary effects to prevent or reduce albuminuria and decline in estimated glomerular filtration rate spurred further investigation into their potential application in DKD. This review summarizes the current understanding of mechanisms by which SGLT2 inhibitors block glucose reabsorption in the proximal tubule and improve systemic glucose homeostasis, the hypothesized mechanisms for kidney-protective effects of SGLT2 inhibition, and current recommendations for use of this class of antihyperglycemic agents in diabetic patients with low estimated glomerular filtration rates. Results of ongoing clinical trials in patients with DKD are eagerly awaited to expand knowledge of how SGLT2 inhibitors might be used for prevention and treatment.

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Introduction

The overall prevalence of diabetes has nearly quadrupled since 1980, and the number of people living with diabetes mellitus ("diabetes") worldwide continues to expand at an unprecedented rate.[1] In 2015, the global estimated prevalence of diabetes was 415 million cases; by 2040, prevalence is projected to reach 642 million.[2]

Despite improvements in diabetes care, approximately one-third of patients with type 1 diabetes and nearly half those with type 2 diabetes develop diabetic kidney disease (DKD).[3-5] In either type 1 or type 2 diabetes, DKD is typically diagnosed by the presence of severely increased albuminuria (albumin-creatinine ratio > 300 mg/g) or moderately increased albuminuria (albumin-creatinine ratio of 30-300 mg/g) associated with diabetic retinopathy.[6] Additionally, for type 1 diabetes, more than 10 years' duration of diabetes is required for the latter diagnostic criteria.[6] Nearly half of all cases of end-stage kidney disease are attributed to DKD, making it by far the leading cause of permanent kidney failure in the United States and throughout the world.[7] As such, DKD is on track to surpass all other diabetic complications in terms of attributable morbidity and mortality.[5-9] The swift increase in DKD prevalence has exacted a significant human toll as well. Individuals who have both diabetes and DKD carry 3- to 12-fold higher mortality risk than those with only diabetes, and 90% of patients with DKD will die before progressing to end-stage kidney disease.[9]

Despite optimal diabetes care, including good glycemic control and treatment of hypertension with renin-angiotensin system inhibition, large residual risk for DKD development and progression remains.[9] Moreover, treatment of hyperglycemia in individuals who develop DKD is complicated by alterations in drug responses, absorption, distribution, and metabolism, as well as alterations of the kidney's role in glucose homeostasis.[10,11] Sodium/glucose co-transporter 2 (SGLT2) inhibitors, an emerging class of new antihyperglycemic medications, have shown encouraging results for improving outcomes of DKD in clinical trials for cardiovascular safety.

SGLTs in the Kidney and Glucose Metabolism

The kidney plays an integral role in glucose homeostasis by 3 mechanisms: uptake and consumption of circulating glucose, release of glucose by gluconeogenesis, and reabsorption of glucose from the glomerular filtrate.[10,12] Of these, reabsorption is thought to be a principal contribution to maintaining systemic glucose homeostasis.[12,13] Knowledge of the mechanism of tubular glucose reabsorption was greatly advanced by the identification, cloning, and structural characterization of the sodium/glucose co-transporter 1 (SGLT1) and SGLT2, which exhibit distinct and complementary expression patterns and glucose transport kinetics in the tubular epithelium.[14-18] SGLT2 is expressed almost exclusively in epithelial cells of the proximal convoluted tubule and accomplishes reabsorption of >90% of filtered glucose.[19-22] Glucose that escapes reabsorption by SGLT2 is subsequently resorbed by SGLT1, which is expressed in epithelial cells of the straight descending proximal tubule.[21-26]

Under normoglycemic and moderately hyperglycemic conditions, nearly all filtered glucose undergoes reabsorption in the kidney tubules.[12] The level of hyperglycemia that

precipitates glycosuria (the glycemic threshold) exhibits substantial intraindividual variability in humans, but approximates 180 mg/dL in normoglycemic individuals and may reach up to 200 mg/dL in diabetic patients (Fig 1).[21,27-31] The mechanism underlying an increase in glycemic threshold in diabetes is not well understood. It may be partly driven by compensatory increases in expression, localization, or activity of SGLTs in the tubular epithelium under conditions of chronic hyperglycemia.

This hypothesis is supported by a report that tubular epithelial cells freshly isolated from urine of patients with type 2 diabetes exhibit elevated expression and glucose transport activity of SGLT2 compared with those collected from nondiabetic individuals.[32] Preclinical studies using rat models of type 2 and alloxan-induced diabetes, as well as a mouse model of streptozotocin-induced type 1 diabetes, further corroborate this hypothesis.[33-35] However, studies of human kidney biopsies are conflicting. Some report greater levels of SGLT1 messenger RNA and unchanged SGLT2 expression in kidney tissue from diabetic patients compared to that from nondiabetic patients, while others report unchanged levels of SGLT1 messenger RNA and reduced SGLT2 expression.[36,37] Although diabetes-induced changes in the expression and/or transporter

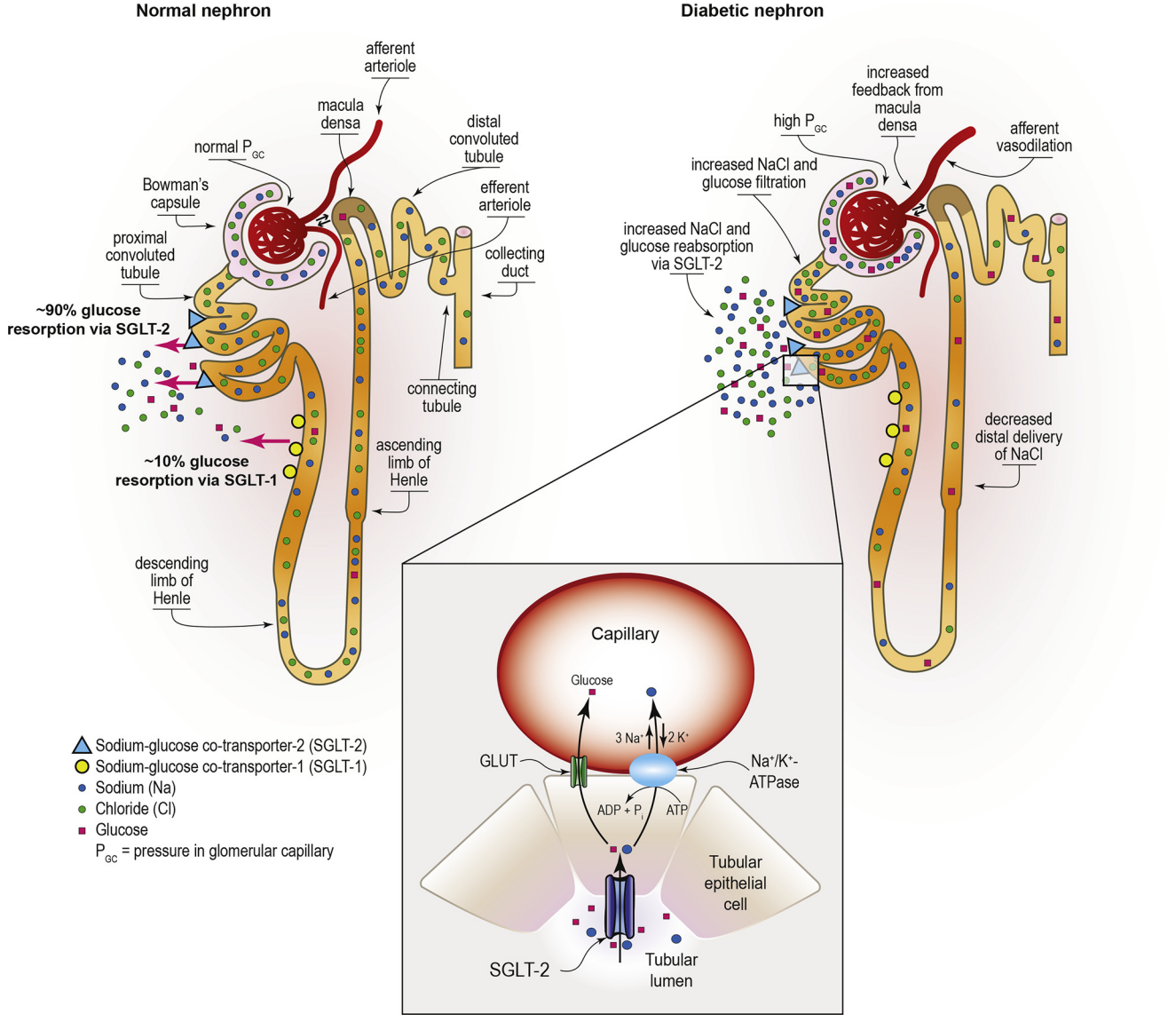

Figure 1. Glucose reabsorption by sodium/glucose co-transporter 1 (SGLT1) and SGLT2 in normal and diabetic kidney. SGLT2, a low-affinity, high-capacity glucose transporter, is expressed apically in epithelial cells of the proximal convoluted tubule and accomplishes reabsorption of ~90% of filtered glucose.[23-26] Approximately 10% of glucose that escapes reabsorption by SGLT2 is subsequently resorbed by high-affinity low-capacity SGLT1, which is expressed apically in epithelial cells of the straight descending proximal tubule.[25,26,41,79,94] To provide the energy required to drive glucose transport against its concentration gradient, both SGLT2 and SGLT1 couple glucose transport across the apical cell membrane to the electrochemical gradient generated by active sodium-potassium transport by adenosine triphosphatase on the basolateral membrane.[26,79]