Sodium Glucose Cotransporters and Persistent Hyperglycemia in Type 2 Diabetes

By John A. Welz, MPH

Research continues to focus on advances that shed light on the functional mechanisms of type 2 diabetes. One such advance is the paradigm of the Ominous Octet, a group of 8 pathophysiologic defects that play important roles in the development of glucose intolerance in type 2 diabetes.1 Formerly, the focus was on 3 core defects: insulin resistance in the muscle; insulin resistance in the liver; and pancreatic β-cell failure.1 The Ominous Octet includes these 3 core defects, along with 5 additional contributors to insulin resistance: the fat cell (accelerated lipolysis); gastrointestinal tract (incretin deficiency/resistance); pancreatic α-cell (hyperglucagonemia); kidney (increased glucose reabsorption); and brain (insulin resistance).1

This article focuses on the role of glucose reabsorption in the kidney in regulating plasma glucose levels, and in particular, the contributing role of sodium glucose cotransporters (SGLTs) in persistent hyperglycemia in type 2 diabetes.

The Role of Glucose Reabsorption in the Kidney

Glycemia is controlled by a complex cluster of interacting physiologic mechanisms, including pancreatic function, glucose formation in the liver and kidney, peripheral glucose uptake, and the reabsorption of glucose in the kidney, which plays an important role in regulating plasma glucose levels.1,2 Each day, the kidney filters approximately 180 L of plasma.1,2 In healthy individuals, this 180 L of filtered plasma contains approximately 162 g of glucose.1,2 Virtually all of the filtered glucose is reabsorbed in the proximal tubules through 2 SGLTs—SGLT1 and SGLT2—in order to meet the energy demands of the body.1 The SGLTs play a central role in the transport and translocation of glucose across epithelial membranes.3 Together, SGLT1 and SGLT2 ensure that all of the filtered glucose entering the kidney returns to the bloodstream, and is not excreted in the urine.1,3

SGLT2: Pivotal Role in Glucose Reabsorption

Of the 2 transporters in the kidney, SGLT2 performs a majority of the transport work, medi-
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In healthy individuals, 90% of the filtered glucose is reabsorbed in the proximal tubules by SGLT2.

Type 2 Diabetes: A Dysregulation of Glucose Homeostasis

Type 2 diabetes is a dysregulation of glucose homeostasis characterized by impaired pancreatic β-cell function, insulin resistance, and persistent hyperglycemia. Insulin resistance and impaired insulin secretion are 2 key contributors to the development of type 2 diabetes. Insulin resistance is already present during prediabetes. Insulin secretion worsens over time, coinciding with a progressive decline in both the function and mass of β-cells.

In recent years, it has been recognized that the onset of β-cell failure occurs earlier and is more severe than previously thought. Similarly, the impairment of insulin’s ability to stimulate glucose uptake and block glucose production occurs at an early stage in the natural history of type 2 diabetes.

While genetic variants that may predispose a person to impaired β-cell dysfunction have been identified, the toxic effects of hyperglycemia (glucotoxicity) and elevated levels of free fatty acids (lipotoxicity) may accelerate or exacerbate this predisposition. In fact, hyperglycemia—marked by chronic elevation of plasma glucose that impairs both insulin action and insulin secretion—plays a key role in the development and progression of the 2 main defects underlying type 2 diabetes: β-cell dysfunction and insulin resistance.
In both the genetic variants of impaired β-cell function and variants arising from glucotoxicity and lipotoxicity, the adverse effects of persistent hyperglycemia result in part when the increased generation of reactive oxygen species (chemically reactive molecules containing oxygen) leads to the activation of oxidative stress.2,6

Hyperglycemia: Negative Impact on β-Cell Function

The direct negative impact of hyperglycemia on β-cell function was demonstrated in experiments on isolated human β-cells.2 In one study, isolated human pancreatic islet cells were cultured for 5 days under normoglycemic conditions (5.5 mmol/L glucose). Other islet cells were alternately exposed to normoglycemic and hyperglycemic conditions (high glucose was 16.7 mmol/L); exposure was alternated every 24 hours for 5 days.6

The researchers found that exposure to intermittent high glucose levels significantly decreased glucose-stimulated insulin secretion.2 Furthermore, intermittent exposure to high glucose levels had several other negative effects on β-cells: activated apoptosis; altered mitochondrial morphology and density volume; and increased intracellular concentration of the oxidative stress marker nitrotyrosine.2,6

Hyperglycemia: Contribution to Insulin Resistance

Pathologically, high glucose levels have been shown to worsen insulin resistance in humans. In a study that examined the mechanisms of hyperglycemia-induced insulin resistance, 8 men with type 1 diabetes were assessed twice: after each subject underwent 24 hours of hyperglycemia (mean blood glucose 20.0 ± 0.3 mM, intravenous [IV] glucose); and also after each subject underwent 24 hours of normoglycemia (mean blood glucose 7.1 ± 0.4 mM, IV saline).7

In this study, hyperglycemia induced a notable decrease in whole body and nonoxidative glucose disposal.7 Following the 24-hour hyperglycemia period, there was a marked decrease in glucose uptake, as evidenced by a 26% reduction in glucose uptake, as evidenced by a 26% reduction in total insulin-stimulated glucose disposal (P <.05) and a 54% reduction in nonoxidative glucose uptake (due primarily to glycogen synthesis [P <.01]), compared with the 24-hour normoglycemia period.7

Persistent Hyperglycemia and Increased Renal Glucose Reabsorption in Type 2 Diabetes

In people without diabetes, the balance between glucose production and glucose utilization is highly regulated, ensuring that only modest fluctuations of plasma glucose concen-
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Conversely, people with type 2 diabetes have an imbalance in glucose production and glucose utilization. This imbalance in type 2 diabetes causes the dysregulation of glucose homeostasis characterized by persistent hyperglycemia. Furthermore, in type 2 diabetes, renal glucose reabsorption is increased. 

As discussed earlier, most of this renal glucose reabsorption occurs via 2 active transporters—SGLT1 and SGLT2—with the vast majority of reabsorption occurring through SGLT2, a transporter expressed almost exclusively in the proximal tubule in the kidney.

Hyperglycemia Increases SGLT2 Transport Activity and Elevates $Tm_G$

In type 2 diabetes, when hyperglycemia leads to an increase in the upregulation of SGLT2 proteins and a corresponding rise in SGLT2 transport activity, the threshold of glucose filtration also increases (Figure 2). Consequently, more glucose is reabsorbed back into the bloodstream, which in turn affects the threshold for glucose excretion in the urine. 

In patients with type 2 diabetes, more glucose is reabsorbed into the bloodstream, which leads to increased upregulation of SGLT2 proteins, a corresponding rise in SGLT2 transport activity, and a subsequent change in the threshold for glucose excretion in the urine (glycosuria). 

The dynamics of glucose reabsorption and excretion in the kidney in healthy individuals compared with those with type 2 diabetes are shown in Figure 3. In type 2 diabetes, increased glucose reabsorption into the bloodstream results from elevation of its transport maximum or $Tm_G$, which is also the threshold concentration at which glucose appears in the urine. Furthermore, the diabetic kidney’s increased glucose-reabsorption response appears to be compounded by a corresponding increase in the kidney’s absolute reabsorptive capacity for glucose. In short, the increase in glucose reabsorption helps to perpetuate hyperglycemia, creating a deleterious cycle.

As a result of these changes in renal glucose reabsorption and excretion, glycosuria does not occur in patients with diabetes until blood glucose levels are higher than the levels at which a person with normal glucose tolerance excretes glucose in the urine.

Phlorizin: A Natural Compound that Lowers $Tm_G$

Phlorizin, a natural product and dietary component found in a number of fruit trees, is a dihydrochalcone (a member of the chalcone class of organic compounds). Its use as a tool for renal physiology research spans more than 150 years.

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Figure 3. Glucose Reabsorption and Excretion in the Kidney in Healthy Individuals Compared with Individuals with Type 2 Diabetes

$Tm_G$ indicates glucose transport maximum; T2DM, type 2 diabetes mellitus. Source: Reference 3.
Phlorizin’s principal action is to produce renal glycosuria and inhibit intestinal glucose absorption by affecting SGLTs in the kidney (in the proximal renal tubule) and in the small intestine (in the mucosa).^8^ The binding of phlorizin to SGLT involves 2 major sites: an aglucone binding site on the transporter surface (with the help of a disulfide bridge between extramembranous loops); and the sugar binding/translocation site within the hydrophilic pocket of the transporter.\^4^

**Phlorizin: Effect of Reduced SGLT2 Function on Insulin Sensitivity**

Phlorizin was shown to decrease insulin resistance and correct hyperglycemia in an animal model of type 2 diabetes.\^9^ In a study that evaluated the effects of phlorizin treatment on total body glucose uptake in diabetic (partially pancreatectomized) rats, the administration of phlorizin resulted in normalization of plasma glucose levels without affecting plasma insulin concentrations.\^9^ Moreover, treatment with phlorizin normalized glucose uptake but had no effect on insulin action in normal controls.\^9^ The effect of phlorizin was reversed upon its discontinuation, leading to the reemergence of insulin resistance and hyperglycemia.\^9^ In this animal study, the improvement in insulin action after phlorizin administration was attributed to increased tissue glucose uptake and not to a more effective suppression of hepatic glucose output (phlorizin did not have an effect on hepatic glucose output in either the diabetic or control groups).\^9^

**Genetic Impairment of SGLT2: No Known Clinically Relevant Consequences in Humans**

Familial renal glycosuria (FRG), a rare genetic condition leading to the malfunction or absence of SGLT2, serves as a model for the effects of SGLT2 inhibition. Individuals with FRG have a normal oral glucose tolerance test, as well as normal plasma levels of insulin, free fatty acids, and glycated hemoglobin; however, they exhibit decreased renal glucose reabsorption and increased glycosuria, with excretion of 10 g to 100 g of glucose per day in their urine.\^10^ In short, FRG is characterized by the occurrence of glycosuria in the absence of hyperglycemia and proximal tubular dysfunction.\^10^

Glycosurias have been categorized into specific types, based on the renal threshold for glucose and the TmG.\^10^ In patients with type A FRG, both the renal glucose reabsorption threshold and the maximal rate of TmG are below normal.\^10^ In type B FRG, the renal glucose reabsorption threshold is reduced by the TmG, leading to an abnormal splay of the filtration–reabsorption curve.\^10^ In addition, a complete absence of renal glucose transport was subsequently identified and designated as type O glycosuria.\^10^ FRG is not known to be associated with greater or lesser susceptibility to kidney disease, diabetes, or urinary tract infections than in people without FRG.\^10^ In severe cases (glycosuria >30 g/1.73 m^2^/day), activation of the renin–angiotensin–aldosterone system was reported, and caloric loss interfering with growth was reported in the single individual known to have type O FRG.\^10^ In addition, aminoaciduria has been observed in some cases.\^10^

**Summary**

The SGLTs in the kidney play a pivotal role in glycemic homeostasis. In healthy individuals, the kidney filters approximately 162 g of glucose each day. The vast majority (90%) of the filtered glucose is reabsorbed in the proximal tubules by SGLT2.\^3^ Hyperglycemia contributes to the progression of type 2 diabetes. In type 2 diabetes, hyperglycemia increases the filtered glucose load subsequently increasing glucose reabsorption into the bloodstream.\^3^ This increase in glucose reabsorption helps to perpetuate hyperglycemia, creating a vicious cycle that may worsen the diabetic state.\^1^ Changes in renal glucose reabsorption affects glycemic homeostasis, and may be a hidden contributor to persistent hyperglycemia in type 2 diabetes. Advances in understanding the impact of SGLT2 function on glucose excretion and reabsorption present an entirely new perspective on hyperglycemia in type 2 diabetes—one that warrants continued exploration.\^1^

**References**

About the Author

John A. Welz, MPH, is a medical and managed care writer. With more than 12 years of agency-based consulting and health plan experience, Mr. Welz has expertise in strategic and tactical planning, formulary dossier development, and pharmacoeconomic modeling.

In his previous role as a member of the Health Informatics team at HIP Health Plan of New York (now EmblemHealth), Mr. Welz designed and implemented quality improvement initiatives to support health plan accreditation efforts, directed drug utilization experience analyses, and conducted health outcomes studies.

Mr. Welz has presented original research on smoking cessation, diabetes, and hypertension at national healthcare meetings, and is a member of the American Public Health Association.

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