Novel Hypothesis to Explain Why SGLT2 Inhibitors Inhibit Only 30–50% of Filtered Glucose Load in Humans

Muhammad A. Abdul-Ghani, Ralph A. DeFronzo, and Luke Norton

Inhibitors of sodium-glucose cotransporter 2 (SGLT2) are a novel class of antidiabetes drugs, and members of this class are under various stages of clinical development for the management of type 2 diabetes mellitus (T2DM). It is widely accepted that SGLT2 is responsible for >80% of the reabsorption of the renal filtered glucose load. However, maximal doses of SGLT2 inhibitors fail to inhibit >50% of the filtered glucose load. Because the clinical efficacy of this group of drugs is entirely dependent on the amount of glucosuria produced, it is important to understand why SGLT2 inhibitors inhibit <50% of the filtered glucose load. In this Perspective, we provide a novel hypothesis that explains this apparent puzzle and discuss some of the clinical implications inherent in this hypothesis. ***Diabetes*** **62:3324–3328, 2013**

Despite the irrefutable evidence for the important role of hyperglycemia in the development of diabetic microvascular complications (1,2) and the large number of antidiabetes agents available for the management of individuals with type 2 diabetes mellitus (T2DM), the majority of subjects with T2DM still manifest suboptimal glycemic control (3). Over half of all patients with T2DM in the U.S. fail to meet the American Diabetes Association treatment goal of HbA_{1c} <7%, and a smaller number of subjects achieve the American College of Clinical Endocrinologists goal of HbA_{1c} <6.5% with existing therapies (3). Progressive β-cell failure, weight gain, and hypoglycemia are some of the obstacles for the achievement of optimal glycemic control (HbA_{1c} ≤6.5) in patients with T2DM. Therefore, additional antidiabetes agents that are effective in lowering the plasma glucose concentration without weight gain and hypoglycemia are required for the treatment of T2DM individuals. Sodium-glucose cotransporter 2 (SGLT2) inhibitors represent a novel class of antihyperglycemic drugs that inhibit glucose reuptake in the kidney and are under clinical development for the treatment of T2DM (4). Dapagliflozin is approved in Europe, and canagliflozin recently was approved in the U.S. This class of drugs lowers the plasma glucose concentration by inhibiting SGLT2, leading to glucosuria. Because SGLT2 inhibitors produce urinary glucose loss, they also promote weight loss. Since the mechanism of action of the SGLT2 inhibitors is independent of insulin action and insulin secretion, they lower the plasma glucose concentration without increasing the risk of hypoglycemia. Moreover, because of this unique mechanism of action, SGLT2 inhibitors are effective in lowering the HbA_{1c} at all stages of diabetes (5), and they can be used in combination with all other antihyperglycemic agents including insulin (6).

The efficacy of SGLT2 inhibitors to reduce the HbA_{1c} and promote weight loss is highly dependent upon the amount of glucosuria produced by these agents. Clinical studies have demonstrated that the glucosuria produced by these agents is less than would be expected from the inhibition of SGLT2. In this Perspective, we suggest an explanation for this paradox, discuss some of the clinical implications of this explanation, and suggest mechanisms to improve the clinical efficacy of SGLT2 inhibitors.

THE PARADOX

In healthy normal glucose-tolerant individuals, the kidney filters ~180 g (FPG 100 mg/dL × 180 L/day) of glucose daily. All of the filtered glucose is reabsorbed by the kidney in the proximal tubule and returned to the circulation (Fig. 1) by an SGLT mechanism (7). Two SGLTs are responsible for the glucose reabsorption in the proximal tubule: SGLT1 and SGLT2 (7). They are located in the luminal membrane of the proximal tubule cells and couple sodium and glucose transport from the glomerular filtrate into the tubular cell. The sodium electrochemical gradient generated by active sodium transport provides the energy required for glucose transport. SGLT1 is located in the more distal S3 segment of the proximal tubule and has high affinity (Km = 0.4 mmol/L) but low capacity for glucose transport. Conversely, SGLT2 is located in the S1 and S2 segments of the proximal tubule and has a low affinity (Km = 2 mmol/L) but high capacity for glucose transport. The SGLT2 transporter is expressed exclusively in the proximal tubule of the kidney, while SGLT1 primarily is expressed in the kidney and the gut, where it is responsible for the majority of glucose and galactose absorption in the gut. Under physiologic conditions, SGLT2 is responsible for the absorption of ~80–90% of the filtered glucose load, while the remaining 10–20% of filtered glucose is taken up by the SGLT1 transporter (4,7).

Because SGLT2 is responsible for >80% reabsorption of the filtered glucose load, one would expect that inhibiting SGLT2 will produce massive glucosuria (>80% of filtered glucose load or >145 g glucose/24 h). All SGLT2 inhibitors produce a dose-dependent glucosuria. However, the maximal amount of glucose excreted in the urine is far lower than that taken up by SGLT2 in normal glucose tolerant (NGT) individuals and does not exceed 35–40% of the filtered glucose load. For example, 20 mg dapagliflozin produced ~55 g urinary glucose excretion (UGE) in 24 h in NGT individuals compared with ~145 g/day taken up by

From the Division of Diabetes, University of Texas Health Science Center at San Antonio, San Antonio, Texas.
Corresponding author: Muhammad A. Abdul-Ghani, abdulghani@uthscsa.edu.
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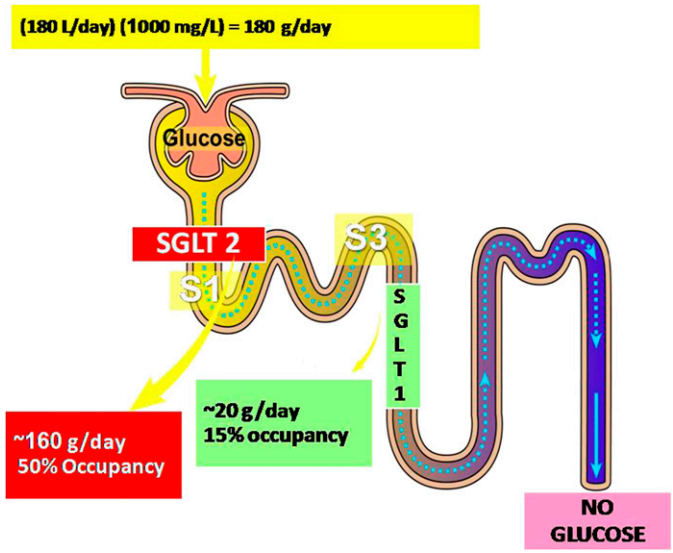

FIG. 1. Renal glucose reabsorption in the proximal tubule in NGT individuals under physiologic conditions.

SGLT2 under physiologic conditions (8). Moreover, further increase in dapagliflozin dose does not further increase UGE (8). Thus, 500 mg dapagliflozin caused 58 g UGE/24 h. Similar observations have been reported with other SGLT2 inhibitors currently under clinical development (9). Since, under physiologic conditions, SGLT2 is responsible for >80% of glucose reabsorption (>145 g/24 h), it is anticipated that specific SGLT2 inhibitors will produce >145 g of glucosuria in NGT individuals. So, why then do all SGLT2 inhibitors produce only ~50–60 g glucosuria, which represents <50% of the glucose-filtered load?

Several explanations have been proposed to explain this paradox (10). However, none are completely satisfactory.

Physiologic considerations. Clinical studies that have measured the maximal renal glucose reabsorption capacity (T_{max}) have reported a value of ~300–350 mg/min (11). It should be emphasized that this T_{max} represents the sum of maximal transport capacity of SGLT1 plus SGLT2. In normal individuals, the filtered glucose load is less than the maximal glucose transport capacity (~180 g/day or ~124 mg/min). Thus, all of the filtered glucose is taken up in the proximal tubule. Glucosuria is produced only if the filtered glucose load exceeds 350 mg/min, as may occur in individuals with poorly controlled diabetes. Under these conditions, the T_{max} is exceeded and all of the filtered glucose in excess of the T_{max} is excreted in the urine. The plasma glucose concentration at which the filtered glucose load reaches the T_{max} is called the threshold, and in NGT individuals the threshold is ~180 mg/dL. Above the threshold, UGE rate increases linearly and parallels the filtered load. However, the reabsorption and excretion curves display a nonlinear transition as the T_{max} for glucose is approached. This "rounding" of the curves is termed splay and has been explained by heterogeneity in the T_{max} of individual nephrons or glomerulotubular imbalance (4). Thus, the actual plasma glucose concentration at which glucosuria is observed (observed threshold) is lower than the theoretical threshold, which represent the T_{max}. In healthy individuals, the observed threshold is ~180 mg/dL while based upon the reported T_{max} the theoretical threshold is ~280 mg/dL.

Another important physiologic consideration that must be taken into account is the anatomical location of the two transporters. As stated earlier, SGLT2 is located in the proximal part of the proximal tubule (S1 and S2 segments), while SGLT1 is located in the distal part (S3) of the proximal tubule. Thus, the glomerular filtrate first passes through SGLT2, where the majority of filtered glucose (~80–90%) is taken up. Micropuncture studies have confirmed that by the time glomerular filtrate reaches the distal part of the proximal tubule, ~80–90% of filtered glucose has been reabsorbed (12). Thus, by the time glomerular filtrate reaches SGLT1 in the S3 segment, only a small amount of the filtered glucose remains to be "cleaned up" by the high-affinity SGLT1 transporter.

IS THERE REALLY A PARADOX?

Under conditions of complete SGLT2 inhibitions, SGLT1 remains the sole mechanism of renal glucose reabsorption. Therefore, the amount of glucose excreted in the urine after maximal SGLT2 inhibition will be highly dependent upon the maximal SGLT1 glucose transport capacity and will equal the glucose filtration load minus the SGLT1 maximal glucose transport capacity. Therefore, to obtain an estimate of the amount of glucose expected to be excreted in the urine with complete SGLT2 inhibition, it is necessary to know the maximal glucose transport capacity of SGLT1.

Maximal SGLT1 transport capacity in humans. T_{max} represents the maximal glucose transport capacity of both SGLT1 and SGLT2. Thus, under conditions in which the SGLT2 transporter is completely inhibited, the renal T_{max} represents the maximal SGLT1 glucose transport capacity (Fig. 2). Based upon this reasoning, the renal T_{max} can be estimated in genetically manipulated mice lacking SGLT2 transporters, e.g., SGLT2 knockout mice, and in subjects who received a maximal dose of SGLT2 inhibitor. If one assumes that inhibition of SGLT2 with a specific SGLT2 inhibitor completely blocks the transporter and produces maximal glucosuria, one can derive a reliable estimate of maximal SGLT1 glucose transport capacity. Studies in NGT individuals have reported that the maximal amount of urinary glucose excreted in the urine with dapagliflozin (8) and

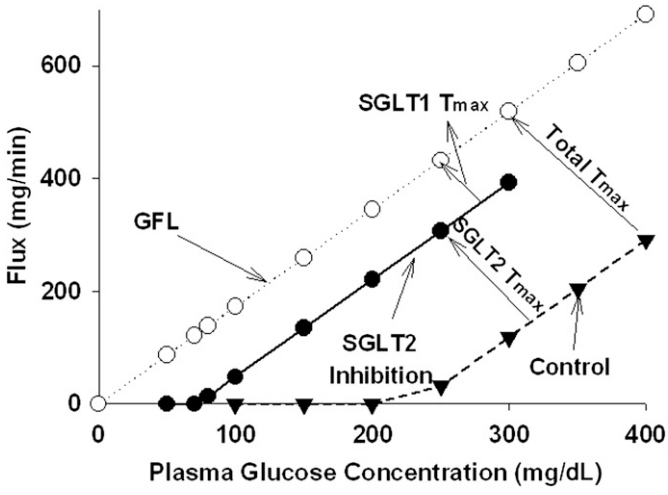

FIG. 2. Relationship between glucose filtration load (GFL) and UGE and the plasma glucose concentration under physiologic conditions and during maximal inhibition of SGLT2.

canagliflozin (9) is 55–60 g/24 h and that a 10-fold increase in the drug dose does not cause any further increase in glucose excretion. Based upon the fasting plasma glucose concentration and glomerular filtration rate reported in these studies, the maximal SGLT1 glucose transport capacity (assumes that SGLT2 is completely inhibited) in NGT individuals can be estimated at ~120 g/24 h (180 g glucose is filtered minus ~60 g UGE). Moreover, the plasma glucose threshold for glucosuria in NGT individuals was reduced by a maximal dose of canagliflozin (300 mg) to ~60 mg/dL (9). This value of plasma glucose threshold for glucosuria represents 108 g renal glucose reuptake/24 h. That the observed glucose threshold is somewhat lower than the theoretical plasma glucose threshold, which represents the T_{max} values, likely means that the 108 g/24 h is an underestimation of SGLT1 maximal glucose transport capacity and indicates that a value of ~120 g/24 h represents a realistic value for the maximal glucose transport capacity of SGLT1. This value of SGLT1 T_{max} represents ~25–30% of the total renal T_{max}.

Glucose transport capacity has been measured in different parts of the rabbit proximal tubule and reported to be 12.9 ± 1.1 and 7.9 ± 0.5 pmol/min/mm^2 for the proximal (S1) and distal (S3) parts (13). Immunohistochemical studies documented the absence of SGLT2 in the distal part of the proximal tubule. Thus, it is likely that the transport capacity of the distal part of the proximal tubule represents the transport capacity of SGLT1. These observations are consistent with the estimate that SGLT1 contributes ~30% to the maximal renal glucose reabsorption capacity. Since renal T_{max} equals ~450 g/24 h, these estimates suggest that the SGLT2 T_{max} is ~300–320 g/day, while SGLT1 T_{max} is ~120–140 g/24 h. This estimate of the SGLT1 T_{max} is consistent with that based upon the amount of glucosuria produced by maximal dose of a SGLT2 inhibitor. Moreover, since under physiologic conditions SGLT2 is responsible for the reabsorption of ~150–160 g glucose/24 h, this estimate of SGLT2 T_{max} indicates that, under physiologic conditions, SGLT2 operates at 50% of its maximal transport capacity, which is consistent with the transporter physiologic occupancy reported recently with direct measurement of glucose flux through SGLT2 (14). The above discussion is consistent with a value of ~120 and ~320 g/24 h for T_{max} of SGLT1 and SGLT2, respectively. These values indicate that by the time the renal filtrate reaches the S3 segment, only ~15–20 g glucose (out of 170–180 g filtered) is left in the glomerular filtrate and is "cleaned up" by SGLT1. Thus, under physiologic conditions SGLT1 operates at only 10–15% of its maximal transport capacity (Fig. 1).

How do SGLT2 inhibitors affect renal glucose reabsorption? Under conditions of complete SGLT2 inhibition, e.g., with maximal dose of SGLT2 inhibitor or in SGLT2 knockout mice, all of the filtered glucose reaches the distal part of the proximal tubule, and, as a result, the SGLT1 transporter is forced to operate in full capacity. This dictates that only the amount of filtered glucose that is in excess of the SGLT1 maximal transport capacity (~120 g/day) will be excreted in the urine. Thus, a maximal dose of SGLT2 inhibitor will produce only 50–60 g glucosuria/day in NGT individuals (180 g filtered − 120 g reabsorbed by SGLT1) (Fig. 3), which is much less than the amount taken up by SGLT2 under physiologic conditions (~140–160 g/24 h).

Because of the anatomical location of SGLT1, under physiologic conditions, it operates at submaximal transport capacity (~10–15%) and, therefore, is responsible for reabsorption of <20% of the filtered renal glucose load. However, under conditions when SGLT2 is completely inhibited, e.g., maximal dose of SGLT2 inhibitor or SGLT2 knockout, SGLT1 is forced to reabsorb glucose at its maximum capacity. As a result, the amount of glucose excreted in the urine is significantly less than that taken up by the SGLT2 transporter under physiologic conditions.

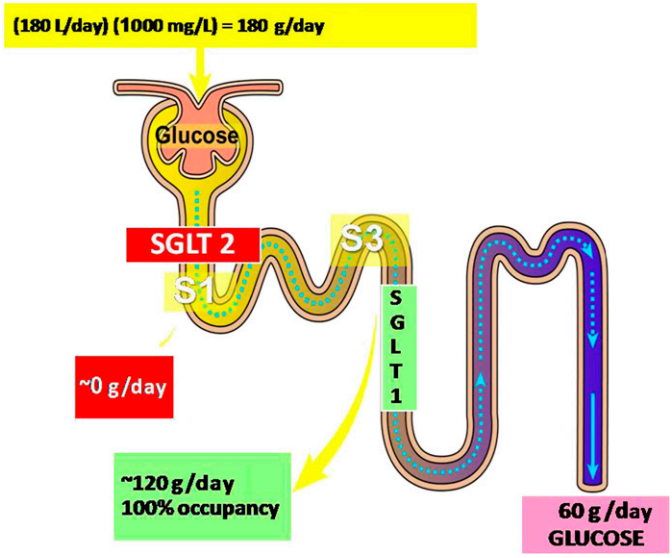

FIG. 3. Renal glucose reabsorption in the proximal tubule in NGT individuals under complete SGLT2 inhibition.

IS THERE EXPERIMENTAL EVIDENCE IN SUPPORT OF THIS HYPOTHESIS?

In the following discussion, we will make several predictions based upon the hypothesis presented above, and we will contrast these predictions with published findings in order to test the validity of this hypothesis.

Because the renal filtered glucose load in NGT individuals (~170 g/day) exceeds the maximal SGLT1 transport capacity, we anticipate that under hyperglycemic conditions, the amount of UGE caused by SGLT2 inhibition

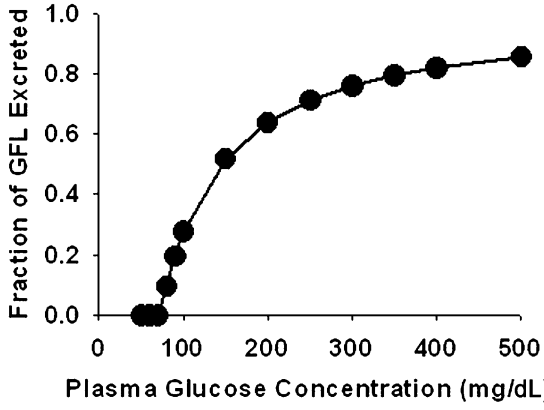

FIG. 4. Predicted relationship between the fraction of filtered glucose excreted in the urine and the plasma glucose concentration during maximal inhibition of SGLT2. The maximal SGLT1 transport capacity was estimated at 120 g/day (see text for details). GFL, glucose filtration load.

will increase linearly with the filtered glucose load. Thus, the fraction of the filtered glucose load that is excreted in the urine will increase with the increase in plasma glucose concentration (Fig. 4). This prediction is consistent with the relationship between the fractional excretion of glucose and the amount of glucose that is filtered (which reflects the level of plasma glucose concentration) in SGLT2 knockout mice. Vallon et al. (12) reported that in SGLT2 knockout mice, the fraction of filtered glucose excreted in the urine increased linearly with the increase in the amount of filtered glucose such that under hyperglycemic conditions, the fractional excretion of glucose can reach as high as 90%.

Conversely, under hypoglycemic conditions that decrease the filter glucose load below the SGLT1 maximal transport capacity, SGLT2 inhibition will produce no glucosuria. This prediction is consistent with the observation by Nagata et al. (15), who reported that a maximal dose of tofogliflozin produced no glucosuria in mice when the plasma glucose concentration was clamped at ~50 mg/dL with insulin infusion. Conversely, phlorizin, which inhibits both SGLT1 and SGLT2, produced significant glucosuria at the same plasma glucose concentration (i.e., 50 mg/dL).

We suggest that SGLT2 inhibitors force SGLT1 to reabsorb glucose at its maximum capacity. Therefore, we would anticipate that, under conditions of complete SGLT2 inhibition, inhibition of SGLT1 will produce marked glucosuria. This prediction is consistent with the results reported by Powell et al. (16) who demonstrated that SGLT2 knockout mice manifest glucosuria which equals ~30% of filtered glucose. However, breeding SGLT2 knockout mice with mice lacking SGLT1 to create the double (SGLT1 and SGLT2) knockout mouse resulted in a threefold greater glucosuric effect compared with that observed in the SGLT2 knockout mouse (747 vs. 224 mg/day). Of note, mice lacking only SGLT1 manifested only a small, nonsignificant amount of glucosuria (<15 mg/day). These results indicate that, in the presence of SGLT2, the contribution of SGLT1 to renal glucose reabsorption is minimal. Conversely, under conditions of SGLT2 inhibition, elimination of renal glucose reabsorption by SGLT1 profoundly enhances UGE. There are no data in human regarding the expression of SGLT1 under conditions of SGLT2 inhibition. However, in mice with deletion of SGLT2, e.g., SGLT2 knockout mice, there is an ~30% decrease in SGLT1 expression. Of note, the SGLT1 knockout mouse provides an opportunity to definitively test the present hypothesis by comparing the amount of glucosuria produced with a SGLT2 inhibitor in SGLT1 knockout mice versus that in wild-type animals. We anticipate that glucosuria produced with a maximal dose of SGLT2 inhibitors in wild-type mice will represent only ~30% of renal glucose excretion, while in SGLT1 knockout mice, SGLT2 inhibitors will result in UGE, which approximates the filter glucose load.

CLINICAL IMPLICATIONS

Based upon our hypothesis, the fraction of filtered glucose excreted by SGLT2 inhibitors will increase with the increase in the plasma glucose concentration (Fig. 4). Therefore, we anticipate that the clinical efficacy of SGLT2 inhibitors will be greater in subjects with a high HbA_{1c} compared with those with low HbA_{1c}. Consistent with this, the decrease in HbA_{1c} observed with dapagliflozin (5 mg) in subjects with HbA_{1c} 10–12% (mean HbA_{1c} = 10.8%) was fivefold greater (2.65 vs. 0.55%) compared with that in subjects with a mean HbA_{1c} ~8.0% (17). This can explain the relatively modest decrease in HbA_{1c} observed in clinical studies that had recruited subjects with a relatively low HbA_{1c} (mean 7.5–8.0%) (18).

TABLE 1
IC_{50} of SGLT2 inhibitors to human SGLT1 and SGLT2 transporters

Agent	IC_{50} for SGLT2	IC_{50} for SGLT1	SGLT2 selectivity (fold)
Phlorizin	34.6	210	6
Tofogliflozin	2.9	8,444	2,912
Empagliflozin	3.1	8,300	2,680
Luseogliflozin	2.26	3,990	1,770
Dapagliflozin	1.12	1,391	1,242
Ipragliflozin	7.38	1,876	254
Canagliflozin	4.4	683	155
LX4211	1.8	36	20

Because of the potential gastrointestinal side effects associated with SGLT1 inhibition, pharmaceutical companies have selected agents with greater selectivity for SGLT2 over SGLT1 for clinical development. As demonstrated in Table 1, the selectivity of SGLT2 inhibitors under clinical development is >100-fold greater for SGLT2 compared with SGLT1 (the ratio between half-maximal inhibitory concentration (IC_{50}) for SGLT1/SGLT2 >100). Based upon our hypothesis, the amount of glucosuria produced with sole inhibition of SGLT2 would be expected to be markedly smaller than the amount of glucose reabsorbed by SGLT2 under physiologic conditions. However, the combination of SGLT1 plus SGLT2 inhibition would be expected to produce a robust glucosuria and greater decrease in the plasma glucose concentration. Figure 5 depicts the fold increase in glucosuria in relationship to percent inhibition of SGLT1 activity. We recognize that complete inhibition of SGLT1 will produce severe gastrointestinal side effects, which may preclude the clinical utility of a potent combined SGLT1/SGLT2 inhibitor, e.g., phlorizin. However, a potent SGLT2 inhibitor that only partially inhibits SGLT1 can be free of gastrointestinal side effects. With respect to this, studies with canagliflozin (19) and LX4211 (20), which partially inhibit gut SGLT1, were not associated with gastrointestinal side effects. Moreover, low-dose (12.5 mg) acarbose, which inhibits glucose absorption via a different mechanism and is tolerated by T2DM individuals, produces an ~30% decrease in the rate

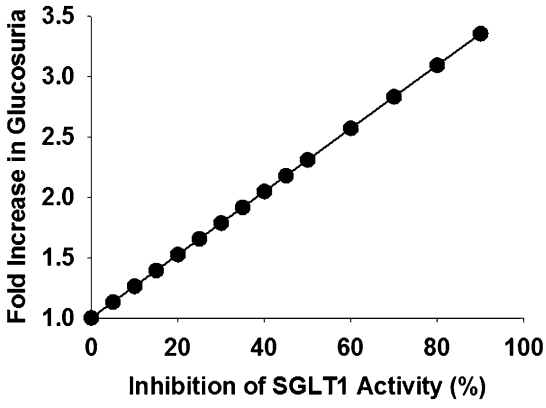

FIG. 5. Predicted fold increase in the level of glucosuria produced by SGLT2 inhibitors in relation to the percent inhibition of SGLT1 activity.

of intestinal glucose appearance in the systemic circulation (21). Thus, we speculate that similar inhibition of glucose absorption by the inhibition of SGLT1 activity (i.e., 30%) is likely to be clinically well tolerated. Based upon the model that we have presented, an SGLT2 inhibition that is capable of inhibiting 30% of SGLT1 transport capacity will increase the amount of glucosuria by ~80% compared with a highly specific SGLT2 inhibitor. Thus, an SGLT2 inhibitor with a lower IC_{50} for SGLT1 (such that the drug produces partial inhibition of SGLT1, i.e., ~30%) will profoundly augment the ability of SGLT2 to produce glucosuria and lower the plasma glucose concentration while avoiding potential gastrointestinal side effects. Moreover, because of the important role SGLT1 in intestinal glucose absorption, partial inhibition of SGLT1 will *1*) produce an "acarbose-like effect" and ameliorate postprandial hyperglycemia (21) and *2*) result in more food ingredients reaching the colon with stimulation of glucagon-like peptide-1 (GLP-1) secretion. A recent 24-week clinical trial has reported an 11 and 20% increase in fasting and postprandial GLP-1 levels in newly diagnosed T2DM individuals receiving a mean of 268 mg acarbose/day (22). Of note, a similar increase in plasma GLP-1 levels has been reported in subjects receiving LX4211 (23). Thus, the combination of dipeptidyl peptidase-4 inhibitor with such a dual SGLT1/SGLT2 inhibitor will also activate the incretin axis and would have a robust effect in lowering the plasma glucose concentration and body weight (23). It remains to be seen whether further increase in glucosuria will affect the rate of urinary and genital infections caused by SGLT2 inhibitors or how the dual SGLT1/SGLT2 activity is affected by renal function.

In summary, why do SGLT2 inhibitors produce UGE, which is <50% of the filtered glucose load? It is simply because they are specific SGLT2 inhibitors. Under physiologic conditions, SGLT1 operates at submaximal transport capacity. Complete inhibition of SGLT2 forces SGLT1 to reabsorb glucose in full capacity, and therefore, only the fraction of filtered glucose that escapes SGLT1 will be excreted in the urine. Thus, we anticipate that future SGLT2 inhibitors with the ability to partially inhibit SGLT1 will produce more robust glucosuria compared with highly specific SGLT2 inhibitors.

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REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
3. Hoerger TJ, Segel JE, Gregg EW, Saaddine JB. Is glycemic control improving in U.S. adults? Diabetes Care 2008;31:81–86
4. Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocr Rev 2011;32:515–531
5. Zhang L, Feng Y, List J, Kasichayanula S, Pfister M. Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus: effects on glycaemic control and body weight. Diabetes Obes Metab 2010;12:510–516
6. Clar C, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012;2:1–12
7. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev 2011;91:733–794
8. Komoroski B, Vachharajani N, Boulton D, et al. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. Clin Pharmacol Ther 2009;85:520–526
9. Sha S, Devineni D, Ghosh A, et al. Canagliflozin, a novel inhibitor of sodium glucose co-transporter 2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. Diabetes Obes Metab 2011;13:669–672
10. Liu JJ, Lee T, DeFronzo RA. Why Do SGLT2 inhibitors inhibit only 30-50% of renal glucose reabsorption in humans? Diabetes 2012;61:2199–2204
11. Farber SJ, Berger EY, Earle DP. Effect of diabetes and insulin of the maximum capacity of the renal tubules to reabsorb glucose. J Clin Invest 1951;30:125–129
12. Vallon V, Platt KA, Cunard R, et al. SGLT2 mediates glucose reabsorption in the early proximal tubule. J Am Soc Nephrol 2011;22:104–112
13. Barfuss DW, Schafer JA. Differences in active and passive glucose transport along the proximal nephron. Am J Physiol 1981;241:F322–F332
14. Hummel CS, Lu C, Loo DD, Hirayama BA, Voss AA, Wright EM. Glucose transport by human renal Na+/D-glucose cotransporters SGLT1 and SGLT2. Am J Physiol Cell Physiol 2011;300:C14–C21
15. Nagata T, Fukazawa M, Honda K, et al. Selective SGLT2 inhibition by tofogliflozin reduces renal glucose reabsorption under hyperglycemic but not under hypo- or euglycemic conditions in rats. Am J Physiol Endocrinol Metab 2013;304:E414–E423
16. Powell DR, DaCosta CM, Gay J, et al. Improved glycemic control in mice lacking Sglt1 and Sglt2. Am J Physiol Endocrinol Metab 2013;304:E117–E130
17. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010;33:2217–2224
18. Abdul-Ghani MA, Norton L, DeFronzo RA. Efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes mellitus. Curr Diab Rep 2012;12:230–238
19. Polidori D, Sha S, Mudaliar S, et al. Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion: results of a randomized, placebo-controlled study. Diabetes Care 2013;36:2154–2161
20. Zambrowicz B, Freiman J, Brown PM, et al. LX4211, a dual SGLT1/SGLT2 inhibitor, improved glycemic control in patients with type 2 diabetes in a randomized, placebo-controlled trial. Clin Pharmacol Ther 2012;92:158–169
21. Wachters-Hagedoorn RE, Priebe MG, Heimweg JA, et al. Low-dose acarbose does not delay digestion of starch but reduces its bioavailability. Diabet Med 2007;24:600–606
22. Zheng MY, Yang JH, Shan CY, et al. Effects of 24-week treatment with acarbose on glucagon-like peptide 1 in newly diagnosed type 2 diabetic patients: a preliminary report. Cardiovasc Diabetol 2013;12:73–81
23. Powell DR, Smith M, Greer J, et al. LX4211 increases serum glucagon-like peptide 1 and peptide YY levels by reducing sodium/glucose cotransporter 1 (SGLT1)-mediated absorption of intestinal glucose. J Pharmacol Exp Ther 2013;345:250–259