Overview on Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors in Glucose Homeostasis

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Normal renal glucose handling

SGLT, sodium-glucose co-transporter

**Majority of glucose is reabsorbed by SGLT2 (90%)**

**Remaining glucose is reabsorbed by SGLT1 (10%)**

**Minimal to no glucose excretion**

I. Glucose homeostasis
II. Renal handling of glucose
III. Metabolic effects of SGLT2 inhibition
IV. Genetic model of SGLT2 inhibition
V. Conclusions
Normal glucose homeostasis

FPG; Fasting plasma glucose
Pathophysiology of T2DM

FPG; Fasting plasma glucose
Hyperglycemia

• =cause of diabetes
• “glucotoxicity” contributes to insulin resistance and impaired insulin secretion
Role of glucotoxicity in the pathophysiology of T2DM

FPG: Fasting plasma glucose
The Kidneys Play an Important Role in the Handling of Glucose

<table>
<thead>
<tr>
<th></th>
<th>Non-DM</th>
</tr>
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<tbody>
<tr>
<td>Total glucose stored in body</td>
<td>~450 g/day</td>
</tr>
<tr>
<td>Glucose utilization</td>
<td>~250 g/day</td>
</tr>
<tr>
<td>• Brain</td>
<td>~125 g/day</td>
</tr>
<tr>
<td>• Rest of body</td>
<td>~125 g/day</td>
</tr>
<tr>
<td>Glucose in (Western) diet</td>
<td>~180 g/day</td>
</tr>
<tr>
<td>Glucose production</td>
<td>~70 g/day</td>
</tr>
<tr>
<td>(gluconeogenesis + glycogenolysis)</td>
<td></td>
</tr>
<tr>
<td>Renal glucose filtration and</td>
<td>~180 g/day</td>
</tr>
<tr>
<td>reabsorption</td>
<td>(720kcal)</td>
</tr>
<tr>
<td>Plasma glucose concentration</td>
<td>~90 mg/dL</td>
</tr>
<tr>
<td>Approximate total blood glucose</td>
<td>4 to 5 g</td>
</tr>
</tbody>
</table>

Altered Renal Glucose Control in Diabetes

- **Gluconeogenesis is increased in postprandial and postabsorptive states in patients with Type 2 DM**
  - Renal contribution to hyperglycemia
  - 3-fold increase relative to patients without diabetes

- **Glucose reabsorption**
  - Increased SGLT2 expression and activity in renal epithelial cells from patients with diabetes vs. normoglycemic individuals
Rationale for SGLT2 inhibitor therapy

• Normalization of the plasma glucose concentration – independent of the mechanism – is a cornerstone of diabetes management
SGLT2 inhibitors -
Mechanism of Action

• Inhibit glucose reabsorption in the renal proximal tubule

• The resultant glucosuria leads to a decline in plasma glucose and reversal of “glucotoxicity”

• Simple, nonspecific
Pathophysiology of T2DM

FPG; Fasting plasma glucose
SGLT2 inhibition in T2DM:
Physiologic consequences

Kidney

FPG 90mg/dL

Muscle

Pancreas

Liver

Fat

Glucosuria

FPG; Fasting plasma glucose
I. Glucose homeostasis

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Normal Renal Glucose Handling

(180 L/day) (1000 mg/L) = 180 g/day

Glucose Transporters

• 2 families of glucose transporters

• Responsible for:
  – Absorption of glucose from small intestine
  – Reabsorption from glomerular filtrate
  – Brain uptake across blood-brain barrier
  – Uptake and release of glucose in all cells

## Two Families of Glucose Transporters

<table>
<thead>
<tr>
<th>GLUT Family</th>
<th>SGLT Family</th>
</tr>
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<tbody>
<tr>
<td>Facilitated glucose transporters</td>
<td>Sodium coupled glucose cotransporter</td>
</tr>
<tr>
<td>Passive, downhill transport</td>
<td>Active transport of glucose</td>
</tr>
<tr>
<td>• GLUT1 (widespread including the kidneys)</td>
<td>• SGLT 1 (brush border of small intestine)</td>
</tr>
<tr>
<td>• GLUT2 (kidneys, pancreas, liver)</td>
<td>• SGLT 2 (proximal tubule)</td>
</tr>
<tr>
<td>• GLUT4 (muscle &amp; adipose tissue)</td>
<td></td>
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</table>

SGLT2 Mediates Glucose Reabsorption In The Kidney

GLUT, glucose transporter; SGLT2, sodium-glucose co-transporter-2.

# SGLT (Sodium-Glucose Cotransporters)

<table>
<thead>
<tr>
<th></th>
<th>SGLT1</th>
<th>SGLT2</th>
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<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td>Mostly intestine, with some kidney</td>
<td>Exclusively kidney</td>
</tr>
<tr>
<td><strong>Sugar specificity</strong></td>
<td>Glucose or galactose</td>
<td>Glucose</td>
</tr>
<tr>
<td><strong>Glucose affinity</strong></td>
<td>High (K_m=0.4 \text{ mM})</td>
<td>Low (K_m=2 \text{ mM})</td>
</tr>
<tr>
<td><strong>Glucose transport capacity</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Role</strong></td>
<td>• Dietary absorption of glucose and galactose (inhibition: osmotic diarrhea)</td>
<td>• Renal glucose reabsorption</td>
</tr>
<tr>
<td></td>
<td>• Renal glucose reabsorption</td>
<td></td>
</tr>
</tbody>
</table>

Lee YJ, Kidney Int Suppl.2007:106:S27
Glucosuria reflects the resorptive capacity of renal proximal tubule

The threshold $T_{m_{\text{glucose}}}$ represents the maximal resorptive capacity of the proximal tubule

$T_{m \text{ glucose}}$; maximal glucose reabsorptive capacity

GFR; glomerular filtration rate

Kinetics of renal glucose handling

- Plasma glucose concentration (mg/dl)
- Glucose reabsorption and excretion

Actual threshold

Theoretical threshold

Reabsorption

Excretion

$T_{\text{max}}$, maximal glucose reabsorptive capacity.


SGLT2, sodium-glucose co-transporter-2; $T_{\text{max}}$, maximal glucose reabsorptive capacity.
Hyperglycemia and Renal Glucose Reabsorption
Renal glucose handling in diabetes

Glucose reabsorption and excretion

Plasma glucose concentration (mg/dl)

100 180 200 240 300

T_{max}

Reabsorption

Excretion

Glucose reabsorption and excretion
Effect of hyperglycemia on the renal Tm for glucose in T2DM and in T1DM

In both T2DM and T1DM patients, the renal Tm for glucose increased

Faber SJ, J Clin Invest 1951;30:125–129


CON, Control; DIAB, Diabetes
Effect of T2DM and insulin on the renal Tm for glucose

Correction of the hyperglycemia resulted in a decrease in Tm for glucose and the appearance of glucosuria.

Farber SJ, J Clin Invest 1951;30:125–129

CON, Control; DIAB, T2DM.
Increased glucose transporter in human renal proximal tubular cells

AMG, alpha-methyl-glucoside
26 Rahmoune H, Diabetes 2005;54: 3427–3434
Summary: Renal tubular glucose reabsorption in diabetes

• In human T1DM and T2DM, the maximum renal tubular reabsorptive capacity (Tm for glucose) is increased

• Cultured human proximal renal tubular cells demonstrate increased SGLT2/GLUT2 mRNA and protein levels and increased glucose transport (AMG).
• An adaptive response to conserve glucose (ie, for energy needs) becomes *maladaptive* in diabetes
  
  – In the presence of hyperglycemia, it would be desirable for the kidney to excrete the excess filtered glucose load to restore normoglycemia.
  
  – In contrast, the diabetic kidney has an increased Tm for glucose, thereby minimizing glucosuria and exacerbating the hyperglycemia.
  
  – Moreover, the ability of the diabetic kidney to conserve glucose may be augmented in absolute terms by an increase in the renal reabsorption of glucose.
I. Glucose homeostasis
II. Renal handling of glucose
III. Metabolic effects of SGLT2 inhibition
IV. Genetic model of SGLT2 inhibition
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SGLT2 inhibitor in development

- 1835 phlorizin isolated from the bark of apple trees → glucosuria
- 1980s; phlorizin acting on SGLT
- 2000; analogs of phlorizin (**gliflozin)

<table>
<thead>
<tr>
<th></th>
<th>SGLT1</th>
<th>SGLT2</th>
<th>Selectivity for SGLT 2 vs. SGLT1</th>
</tr>
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<tbody>
<tr>
<td>Phlorizin</td>
<td>35.6</td>
<td>330</td>
<td>10</td>
</tr>
<tr>
<td>T-1095</td>
<td>6.6</td>
<td>211</td>
<td>30</td>
</tr>
<tr>
<td>Sergliflozin</td>
<td>9.2</td>
<td>&gt;8000</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>1.1</td>
<td>1390</td>
<td>1200</td>
</tr>
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</table>
Effect of SGLT2 inhibitors on insulin resistance

• Targeting the renal glucose transporter
  → improve glucose homeostasis

Experimental Protocol

• Sprague-Dawley rats ; treatment period=4 weeks
  – GROUP I– sham operated controls
  – GROUP II– partial(90%) pancreatectomy
  – GROUP III– 90% pancreatectomy + phlorizin sc
  – GROUP IV– {90% pancreatectomy + phlorizin sc} – phlorizin
Effects of phlorizin treatment on fasting and fed plasma glucose

![Bar chart showing fasting and fed plasma glucose levels in different conditions: CON, DM, DM + PZN, DM ± PZN.](chart.png)

Rossetti L, J Clin Invest 1987; 79: 1510–1515
Effect of SGLT2 inhibitors on insulin resistance

Experimental Protocol
• a 2-step euglycemic insulin clamp

Correction of hyperglycemia with phlorizin normalized insulin sensitivity in diabetic rats
SGLT2 inhibitors and β-cell function

Experimental Protocol

• Sprague Dawley rats; treatment period=3 weeks
  – Group I-sham operated
  – Group II- partial panx (90%)
  – Group III-partial panx + phlorizin

• Hyperglycemic clamp

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Rossetti, J Clin Invest. 1987; 80(4): 1037–1044
Mechanism of Action of SGLT2 Inhibitors

Inhibition of renal SGLT2
⇒ reversal of hyperglycemia
⇒ reversal of “glucotoxicity”

↑ Insulin sensitivity in muscle

↑ Insulin sensitivity in liver

↓ Gluconeogenesis

↑ Improved beta cell function
I. Glucose homeostasis
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Rationale for SGLT2 Inhibition in Diabetes: Functional Disorders

- Familial renal glucosuria
  - Due to SGLT2 gene mutations

- Intestinal glucose-galactose malabsorption
  - Due to SGLT1 gene mutations
  - Severe diarrhea
    - Suggests major role for SGLT1 in intestinal reabsorption
    - Corrected by removing glucose, galactose, lactose from the diet
  - Mild glucosuria consistent with minor SGLT1 role in renal reabsorption

Familiar Renal Glucosuria

• Autosomal recessive
• Rare disorder of renal glucose transport
• Isolated defect of glucose reabsorption
• Mutations of SGLT2
• Characterized by persistent urinary glucose excretion, with normal plasma glucose concentration
• Urinary glucose excretion varies from a few grams to greater than 100g/day

Familial Renal Glucosuria

<table>
<thead>
<tr>
<th>Presentation</th>
<th>• Asymptomatic</th>
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<tbody>
<tr>
<td></td>
<td>• No hypoglycemia or hypovolemia</td>
</tr>
<tr>
<td>Kidney / bladder</td>
<td>• No tubular dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Normal histology and function</td>
</tr>
<tr>
<td>Complications</td>
<td>• No increased incidence of</td>
</tr>
<tr>
<td></td>
<td>– Chronic kidney disease</td>
</tr>
<tr>
<td></td>
<td>– Diabetes</td>
</tr>
<tr>
<td></td>
<td>– Urinary tract infection</td>
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</tbody>
</table>

2 Types of Familial Renal Glucosuria

<table>
<thead>
<tr>
<th>Type A</th>
<th>Type B</th>
</tr>
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<tbody>
<tr>
<td>• Decreased Tm for glucose</td>
<td>• Exaggerated splay</td>
</tr>
<tr>
<td>• Reduced amount of normal SGLT2 protein</td>
<td>• Reduced affinity of SGLT2 transporter for glucose</td>
</tr>
</tbody>
</table>

Theoretical

Observed

Normal

Type B

Type A

Plasma Glucose Concentration (mg/dL)

Glucose Reabsorption

Analysis of SGLT2 Gene in Patients With Renal Glucosuria

• 23 families analyzed for mutations
• In 23 families, 21 different mutations were detected in SGLT2
• Cause of glucosuria in other 2 families remains unknown

Analysis of SGLT2 gene in patients with renal glucosuria

- 14 of 21 individuals were homozygous or compound heterozygous with severe glucosuria = 15~200 grams/day
- Heterozygous family members had mild glucosuria (up to 4.4 grams/day) or no glucosuria
- Nonsense mutations, missense mutations, and small deletions were scattered over the SGLT2 coding sequence
Renal Glucosuria: 20-Year Follow-up of the Original Patient

• On diagnosis at age 11:
  – 109-140g glucose excreted per day
  – Persistent nocturnal enuresis
  – Polyuria and polydipsia
  – Episodes of polyphagia
  – Marked delay of growth and puberty

• On reevaluation at age 31:
  – Reached a final height of 175cm and weight of 74kg; BP 125/85mmHg
  – No sign of hyperfiltration syndrome or microalbuminuria
  – Continued polyuria 3-5 L/day
  – Creatinine :0.6mg/dL; creatinine clearance;135mL/minute
  – No chronic nephrologic complications observed

V. CONCLUSIONS

- SGLT2 inhibition represents a novel approach to the treatment of Type 2 DM
- Studies in experimental models of diabetes have demonstrated that induction of glucosuria restores normoglycemia and improves beta cell function and insulin sensitivity- reversal of glucotoxicity
- Genetic mutations leading to renal glucosuria have documented the long term safety of SGLT2 inhibition in man