SGLT2 Inhibitors in the Treatment of Type 2 Diabetes Mellitus

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Contents

- SGLT2 in glucose homeostasis

- Clinical Outcome of SGLT2 inhibitors
  - Clinical efficacy
  - Safety issues

- Why aren’t SGLT2 inhibitors more potent?
  - Up-regulation of glucose reabsorption by SGLT1
  - Effect on endogenous glucose production
# SGLT Family & Inhibitors

<table>
<thead>
<tr>
<th>SGLT member</th>
<th>Substrate</th>
<th>Distribution in human tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT1</td>
<td>Glucose, galactose</td>
<td>Intestine, trachea, kidney, heart, brain, testis, prostate</td>
</tr>
<tr>
<td>SGLT2</td>
<td>Glucose</td>
<td>Kidney, brain, liver, thyroid, muscle, heart</td>
</tr>
<tr>
<td>SGLT3</td>
<td>Glucose</td>
<td>Intestine, testis, uterus, lung, brain, thyroid</td>
</tr>
<tr>
<td>SGLT4</td>
<td>Glucose, mannose</td>
<td>Intestine, kidney, liver, brain, lung</td>
</tr>
<tr>
<td>SGLT5</td>
<td>Glucose, galactose</td>
<td>Kidney, trachea, uterus, pancreas</td>
</tr>
<tr>
<td>SGLT6</td>
<td>D-chiro-inositol</td>
<td>Brain, kidney, intestine</td>
</tr>
</tbody>
</table>

![Chemical structures](image)
Renal Tubular Reabsorption of Glucose

Diabetes Metab J 2014;38:261-273
Renal Glucose Handling before & after Sodium-Glucose Cotransporter 2 (SGLT2) Inhibition

- Glucose filtration/reabsorption/excretion (mg/min)
- Plasma glucose (mg/dL)

Diabetic Tm for glucose
SGLT2 inhibition
Normal Tm for glucose
Normal threshold
Diabetic threshold

Diabetes Metab J 2014;38:261-273
Reabsorption of Glucose & SGLT2 Inhibition

Filtered glucose load \( \sim 180 \text{ g/day} \)

SGLT2

\(-90\% \text{ glucose reabsorbed}\)

SGLT1

\(-10\% \text{ glucose reabsorbed}\)

Glucose reabsorption \( >179 \text{ g/day} \)

\[ \text{SGLT2 inhibition} \]

Glucose reabsorption reduced to \( \sim 100–130 \text{ g/day} \)

Hyperglycemia reduced in T2DM

Urine

Urinary glucose excretion \( <0.5 \text{ g/day} \)

\[ \text{SGLT2 inhibition} \]

Urinary glucose excretion increased to \( \sim 50–80 \text{ g/day} \)


Drug Design, Development and Therapy 2014:8 1335–1380
Clinical Efficacy: HbA1c & FPG

Not head-to-head comparison among SGLT2 inhibitors
Clinical Efficacy: BP & Body Weight

![Graph showing changes in SBP and body weight with different treatments.](image-url)
Efficacy in Asian Population

Ji L et al: DOM 2014
Body Weight

Systolic BP

Ji L et al: DOM 2014
Effects in Korean Population

Lee MK et al: DRCP 2013
Safety Issues: Hypoglycemia

Drug Design, Development and Therapy 2014:8 1335–1380
Genital & Urinary Tract Infections
Safety issue: Overview

- Hypoglycemia: rare, except add-on to insulin or insulin secretagogues
- Genital infections: increased especially in women and those with Hx of genital infections, generally mild to moderate
- Urinary tract infection: ?mild increase
- Volume depletion: mild, elderly and those on loop diuretics
- Renal function: small initial decrease → return to baseline
- Fractures, Hepatic safety: no signals
- Malignancy: ?bladder cancer signal with dapagliflozin
- Cardiovascular: small increase in LDL, no signal of CV harm
Why aren’t SGLT2 inhibitors more potent?

**Why Do SGLT2 Inhibitors Inhibit Only 30–50% of Renal Glucose Reabsorption in Humans?**
Jiwen (Jim) Liu, TaeWeon Lee, and Ralph A. DeFronzo

*Diabetes 61:2199–2204, 2012*

**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

*Diabetes 62:3324–3328, 2013*
Hypothesis: SGLT1 compensation for increased distal tubular glucose delivery

Physiologic conditions

Complete SGLT2 inhibition

\[(180 \text{ L/day}) \times (1000 \text{ mg/L}) = 180 \text{ g/day}\]

\[\sim 160 \text{ g/day}
50\% \text{ Occupancy}\]

\[\sim 20 \text{ g/day}
15\% \text{ occupancy}\]

\[\sim 0 \text{ g/day}\]

\[\sim 120 \text{ g/day}
100\% \text{ occupancy}\]

\[60 \text{ g/day}
\text{ GLUCOSE}\]
Why aren’t SGLT2 inhibitors more potent?
(1) Incomplete reduction of glucose reabsorption

- SGLT2 reabsorbs 80-90% of the 160-180g glucose filtered daily
- But SGLT2 inhibitors induce a maximum of 50-80g glycosuria

Hypothesis
- **SGLT1 compensation** for increased distal tubular glucose delivery
- Incomplete exposure of renal SGLT2
- Possible presence of other SGLT/GLUTs

Unanswered question
- Is there a therapeutic role for **dual inhibition of SGLT2/1**?
Why aren’t SGLT2 inhibitors more potent?

(2) Increased endogenous glucose production

Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production

Aurora Merovci, Carolina Solis-Herrera, Giuseppe Daniele, Roy Eldor, Teresa Vanessa Florentino, Devjit Tripathy, Juan Xiong, Zandra Perez, Luke Norton, Muhammad A. Abdul-Ghani, and Ralph A. DeFronzo

Diabetes Division, University of Texas Health Science Center, San Antonio, Texas, USA.


Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients

Ele Fenninni,¹ Elza Muscelli,¹ Silvia Frascerra,¹ Simona Baldi,¹ Andrea Mari,² Tim Heise,³ Uli C. Broedl,⁴ and Hans-Juergen Woerle⁴

¹Department of Clinical and Experimental Medicine, University of Pisa School of Medicine, Pisa, Italy. ²CNR Institute of Biomedical Engineering, Padua, Italy. ³Profil, Neuss, Germany. ⁴Boehringer Ingelheim Pharma GmbH and Co. KG, Ingelheim, Germany.

Dapagliflozin improves muscle insulin sensitivity, but enhances endogenous glucose production.

After two weeks of Dapa Tx

4h hyper-insulinemic euglycemic clamp

continuous insulin infusion for 240min

Blunted suppression of endogenous glucose production by increased glucagon secretion

A 4h hyperinsulinemic euglycemic clamp with $3^{-3}H$-glucose

(continuous insulin infusion for 240min)
Increased glucagon/insulin ratio during chronic administration of dapagliflozin

![Graph showing changes in FPI, fasting plasma glucose, and glucagon/insulin ratio for dapagliflozin-treated and placebo-treated subjects.](image)

Acute and chronic administration of empagliflozin increases endogenous glucose production.

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Acute and chronic administration of empagliflozin increases GLP-1 secretion and decreases FFA.
Hormonal & Glucose Flux Responses to SGLT2 inhibition

- Despite lowering FPG, glucosuria produced by inhibition of SGLT2 stimulated a **compensatory increase in EGP**.

- $\uparrow$Glucagon, $\downarrow$Insulin $\rightarrow$ Blunted suppression of endogenous glucose production $\rightarrow$ Attenuation of the reduction in fasting and prandial glycemia

- Greater $\beta$-cell sensitivity ($\uparrow$GLP-1, $\downarrow$glucose toxicity) is insufficient to reverse these changes.

- Unanswered questions
  - Would **combined incretin therapy + SGLT2 inhibition** reverse these?
Summary

- SGLT2 inhibitors show glucose lowering effects in monotherapy and add-on with metformin, insulin, SU, DPP-4I, or TZDs.

- Body weight reduction and BP-lowering effects were also demonstrated.

- SGLT2 inhibitors could preserve beta-cell function and improve insulin sensitivity, and increased endogenous glucose production & glucagon secretion.

- SGLT2 inhibitors are well tolerated, but increased risks of genital infections and UTIs and rise in LDL-cholesterol level were reported.