Targeting the Kidney in Managing the Patient with Type 2 Diabetes: A New Approach

Houston, Texas
March 10, 2012
Session 5: Targeting the Kidney in Managing the Patient with Type 2 Diabetes: A New Approach

Learning Objectives
1. Discuss the role of the kidney in glucose homeostasis.
2. Describe the contribution of the kidney to the sustained elevated glucose levels observed in individuals with uncontrolled type 2 diabetes.
3. Explain the mechanism of action of therapies that act through the kidney to reduce hyperglycemia in type 2 diabetes.
4. Assess clinical efficacy and safety data, and identify the potential place of therapies that target the kidney in the management of type 2 diabetes.

Faculty

William Cefalu, MD
Douglas L. Manship Professorship in Diabetes
Professor, Chief Nutrition/Chronic Disease
Pennington Biomedical Research Center
Louisiana State University
Baton Rouge, Louisiana

Dr William Cefalu is the Douglas L. Manship, Sr., Professor of Diabetes and section chief of the Joint Diabetes, Endocrinology and Metabolism Program at the Louisiana State University (LSU) School of Medicine/Pennington Biomedical Research Center, in Baton Rouge. Prior to his appointment at the Pennington Center, he served as director of the clinical trials unit at the University of Vermont College of Medicine.

Dr Cefalu received his medical degree from the LSU School of Medicine. He completed his residency, and was chief resident, at the University of California (UC), Irvine, Long Beach VA Medical Center. He received fellowship training in metabolism and endocrinology at the UCLA Center for Health Sciences. Dr Cefalu has served on the medical school faculties at Tulane University and Wake Forest University, where he was director of the Diabetes Comprehensive Care Programs.

Dr Cefalu’s research is active at both the clinical and basic levels. Clinically, he is interested in interventions to improve the metabolic state of individuals with insulin resistance and type 2 diabetes. On a basic level, he is interested in the cellular mechanisms of insulin resistance. In addition, Dr Cefalu serves as director for a National Institutes of Health (NIH)–funded Center for the Study of Botanicals and Metabolic Syndrome at the Pennington Center.

Dr Cefalu has published widely in journals, books, and book chapters, and has edited several textbooks on the management of diabetes. He is also editor-in-chief of Diabetes Care.

Eugenio Cersosimo, MD, PhD
Associate Professor of Medicine
The University of Texas Health Science Center at San Antonio
Medical Director of Clinical Research
Texas Diabetes Institute
San Antonio, Texas

Dr Eugenio Cersosimo is the medical director of clinical research at the Texas Diabetes Institute and an associate professor of medicine at the University of Texas Health Science Center, both in San Antonio. He is board certified in endocrinology, diabetes, and metabolism, and maintains an active practice in the adult outpatient clinic in San Antonio.
Dr Cersosimo graduated from medical school at the Universidade Federal Fluminense in Rio de Janeiro, Brazil, in 1975, and, in 1986, obtained a doctorate in physiology at Vanderbilt University in Nashville. In 1994, he received training in internal medicine and endocrinology, diabetes, and metabolism in the Clinician-Investigator Program at the Mayo School of Graduate Medical Education, in Rochester, Minnesota. He started his academic career as an assistant professor of medicine at the State University of New York at Stony Brook, and, in 2001, transferred to his current position.

Dr Cersosimo has authored more than 60 original manuscripts and has received numerous research grants and awards from nonprofits such as the NIH, the Juvenile Diabetes Foundation, the American Diabetes Association, the Kronkosky Charitable Foundation, and the Howard Hughes Institute, and from various pharmaceutical companies. Presently, he is directly involved in and supervises more than 20 different research projects in areas of his greatest interest, among them glucose regulation, the entero-pancreatic axis, and insulin therapy and insulin resistance, with a focus on cardiovascular and renal complications.

**Faculty Financial Disclosure Statements**

The presenting faculty report the following:

Dr Cefalu reports that he has received grants and research support from Lilly/Amylin, AstraZeneca Pharmaceuticals, and Johnson & Johnson; and that he serves as a consultant for AstraZeneca, Johnson & Johnson, and Haloyme.

Dr Cersosimo reports that he has received honoraria from Takeda Pharmaceuticals, Amylin, and sanofi-aventis.

Dr Cefalu intends to reference unlabeled/unapproved uses of SGLT2 inhibitors in his presentation.

Dr Cersosimo intends to reference unlabeled/unapproved uses of SGLT2 inhibitors in his presentation.

**Education Partner Financial Disclosure Statement**

The content collaborator at Voxmedia reports the following:

John F. Kocsis, PhD, has no financial relationships to disclose.

**Acronym List**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AACE</td>
<td>American Association of Clinical Endocrinologists</td>
</tr>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>GLUT</td>
<td>glucose transporter</td>
</tr>
<tr>
<td>OAD</td>
<td>oral antidiabetic agent</td>
</tr>
<tr>
<td>SGLT</td>
<td>sodium glucose cotransporter</td>
</tr>
<tr>
<td>T2D</td>
<td>type 2 diabetes</td>
</tr>
<tr>
<td>UGE</td>
<td>urinary glucose excretion</td>
</tr>
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</table>

**Suggested Reading List**


**Drug List**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>colesevelam</td>
<td>Welchol</td>
</tr>
<tr>
<td>glimepiride</td>
<td>Amaryl</td>
</tr>
<tr>
<td>glipizide</td>
<td>Glucotrol</td>
</tr>
<tr>
<td>glipizide, metformin</td>
<td>Metaglip</td>
</tr>
<tr>
<td>metformin</td>
<td>Glucophage</td>
</tr>
<tr>
<td>pioglitazone</td>
<td>Actos</td>
</tr>
<tr>
<td>sitagliptin</td>
<td>Januvia</td>
</tr>
</tbody>
</table>

**Question # 1**

- I am ______ in my understanding of the role of the kidney in glucose regulation.
  1. Very Confident
  2. Confident
  3. Somewhat Confident
  4. Unsure/Not Confident

**Question # 2**

- ______ actively transports most of the glucose across the proximal convoluted tubule cells of the kidney.
  1. SGLT 1
  2. SGLT 2
  3. GLUT 1
  4. GLUT 2

**Question # 3**

- I am ______ in my understanding of newer therapies that do not specifically target insulin resistance and impaired insulin secretion in type 2 diabetes.
  1. Very Confident
  2. Confident
  3. Somewhat Confident
  4. Unsure/Not Confident

**Question # 4**

- Potential benefits of the SGLT2 inhibitors in addition to glucose lowering include:
  1. BP lowering
  2. Reduction in LDL-C
  3. Weight loss
  4. BP lowering and weight loss
  5. All of the above

**Question # 5**

- If available, I would most likely use SGLT 2 inhibitors ______ in some of my type 2 diabetes patients.
  1. As monotherapy
  2. In combination with other anti-diabetic agents (not including insulin)
  3. In combination with insulin
  4. 1 and 2
  5. 1 and 3
  6. 1, 2, and 3
  7. I am unsure
  8. I would not use them
The Pathophysiology of Glucose Regulation in the Kidney

Eugenio Cersosimo, MD, PhD
Associate Professor of Medicine
Medical Director, Clinical Research
Texas Diabetes Institute
University of Texas HSC at San Antonio

Contribution of the Kidney to Glucose Homeostasis

I: Glomerular Filtration and Reabsorption
II: Glucose Production (Gluconeogenesis)
III: Glucose Utilization
  - Glycogen storage
  - Lactate formation
  - Glucose oxidation

Renal Handling of Glucose

SGLT-2 Mediates Glucose Reabsorption in the Kidney

Kidney and Glucose Homeostasis

SGLT-1 Mediates Glucose Reabsorption in the Kidney

• Nearly exclusively expressed in renal proximal tubule
• Responsible for ~90% of total renal glucose reabsorption
  • Facilitated glucose transport • glucose concentration gradient
  • Restores glucose to circulation

SGLT-2 is located at S1 proximal tubular cell membrane (lumen):
• Low affinity, high capacity for glucose (Na/K electro-chemical gradient)
• Nearly exclusively expressed in the kidney
• Responsible for ~90% of total renal glucose reabsorption


Glucose uptake & gluconeogenesis

Glucose oxidation

Glycogen synthesis & degradation

Lactate formation

SGLT-1

SGLT-2

Filtrate · Urine
Lumen

SGLT2

Glucose

Na+

K+

Interstitial
Fluid · Blood

Fluid · Blood

Na+

Glucose

SGLT-2 is located at S1 proximal tubular cell membrane (lumen):
• Low affinity, high capacity for glucose (Na/K electro-chemical gradient)
• Nearly exclusively expressed in the kidney
• Responsible for ~90% of total renal glucose reabsorption


SGLT-2 is located at S1 proximal tubular cell membrane (lumen):
• Low affinity, high capacity for glucose (Na/K electro-chemical gradient)
• Nearly exclusively expressed in the kidney
• Responsible for ~90% of total renal glucose reabsorption

RENAL GLUCOSE HANDLING


Renal threshold for glucose reabsorption (TmG) is increased by 20-40% in type 2 diabetes (Farber SJ, et al. *J Clin Invest*. 1951; 30:125-29)

Similar elevations have been reported in type 1 diabetes (Morgensen CE. *Scand J Clin Lab Invest*. 1971;28:101-09)


This represents a maladaptive response in diabetes aimed at conservation of glucose for energy needs

UPREGULATION OF SGLT-2 TRANSPORTER AND ENHANCED GLUCOSE UPTAKE IN T2DM*

Transporter Protein Expression

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2</td>
<td><img src="image" alt="Graph" /></td>
<td></td>
</tr>
<tr>
<td>GLUT2</td>
<td><img src="image" alt="Graph" /></td>
<td></td>
</tr>
</tbody>
</table>

*Primary Cultured Proximal Tubule Epithelial Cells

Healthy Type 2 Diabetes

Rationale for Selective SGLT-2 Inhibition in Diabetes

• Correction of the overactive renal tubular glucose reabsorption rates
• Minimize gastrointestinal side effects associated with SGLT-1 inhibition by nonselective agents
• Potential to cause negative energy balance with "desired" body weight loss and maintenance
• No effect on insulin secretion or risk of hypoglycemia
• Unique and additional mechanism of plasma glucose lowering


RENAL GLUCOSE HANDLING AFTER SGLT-2 INHIBITION

Summary

• The kidney helps to maintain glucose homeostasis by free glomerular filtration and complete tubular reabsorption with simultaneous glucose production and utilization

• SGLT-2 is located in the S1 segment of proximal tubules and is responsible for 90% of all glucose reabsorbed

• Normal renal threshold is reached at plasma glucose concentrations of 180-220 mg/dl; glucosuria follows

• In diabetes, a maladaptive increase in the renal glucose reabsorption threshold contributes to hyperglycemia

• Selective SGLT-2 inhibition could become an important treatment target & play a role in diabetes management

Clinical Data to Date with SGLT 2 Inhibitors

William Cefalu, MD
Douglas L. Manship Sr. Professor of Diabetes
Section Head, Joint Diabetes, Endocrinology and Metabolism Program
LSUHSC School of Medicine &
Pennington Biomedical Research Center

Major Targeted Sites of Oral Drug Classes

Effect of SGLT2 Inhibition (Mode of Action)

SGLT2 Inhibitors in Clinical Development

Calculated 24-hr Mean Renal Threshold for Glucose on Day 1 after Canagliflozin Dosing
Placbo-controlled Pool – Short-Term Period

Events of Hypotension / Hypovolaemia / Dehydration in Dapagliflozin Studies

<table>
<thead>
<tr>
<th></th>
<th>Dapa 2.5 mg N = 814</th>
<th>Dapa 5 mg N = 1145</th>
<th>Dapa 10 mg N = 1193</th>
<th>Pbo N = 1393</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Subjects with an Event</td>
<td>10 (1.2)</td>
<td>7 (0.6)</td>
<td>9 (0.8)</td>
<td>5 (0.4)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6 (0.7)</td>
<td>5 (0.4)</td>
<td>5 (0.4)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
<td>0</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3 (0.4)</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Urine Flow Decreased</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
</tr>
<tr>
<td>Blood Pressure Decreased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Orthostatic Hypotension</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urine Output Decreased</td>
<td>1 (0.1)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
</tr>
</tbody>
</table>

Total Subjects with an event:
- Hypotension: 10 (1.2), 7 (0.6), 9 (0.8), 5 (0.4)
- Syncope: 6 (0.7), 5 (0.4), 5 (0.4), 2 (0.1)
- Dehydration: 3 (0.4), 0, 1 (<0.1), 0
- Urine Flow Decreased: 0, 0, 1 (<0.1), 0
- Blood Pressure Decreased: 0, 0, 0, 0
- Orthostatic Hypotension: 1 (0.1), 2 (0.2), 0, 0
- Urine Output Decreased: 1 (0.1), 0, 0, 1 (<0.1)

Pooled data from placebo-controlled dapagliflozin studies.
FDA Advisory Committee 19th July 2011: http://www.fda.gov

Dapagliflozin not FDA approved

All Phase 2b and 3 Pool, All Cases as of May 2011

Malignant and Unspecified Tumors by Tumor Origin in Dapagliflozin Studies

<table>
<thead>
<tr>
<th>Tumor Origin</th>
<th>N =</th>
<th>Dapa 2.5 mg</th>
<th>Dapa 5 mg</th>
<th>Dapa 10 mg</th>
<th>Pbo</th>
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</thead>
<tbody>
<tr>
<td>Overall Malignancies and Unspecified Tumors</td>
<td>46</td>
<td>29</td>
<td>31</td>
<td>14</td>
<td>16.5</td>
</tr>
<tr>
<td>Bladder * (Updated)</td>
<td>7 (9)</td>
<td>8 (0)</td>
<td>8 (0)</td>
<td>2 (0.1)</td>
<td></td>
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<tr>
<td>Thyroidal and Endocrine</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>1 (&lt;0.1)</td>
<td></td>
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<tr>
<td>Gastrointestinal</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>1 (&lt;0.1)</td>
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<td>Pancreatic</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Hepatobiliary</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Musculoskeletal and Soft Tissue</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Metastases and Skin Unspecified</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
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<tr>
<td>Blood and Lymphatic</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
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<tr>
<td>Skin</td>
<td>16</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td></td>
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<tr>
<td>Renal Tract</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1 (&lt;0.1)</td>
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<tr>
<td>Respiratory and Mediastinal</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
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<td>Gender-specific tumor types:</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Breast (Female)</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
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<tr>
<td>Prostate (Male)</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Female Reproductive (Female)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
| Malignant and Unspecified Tumors by Tumor Origin in Dapagliflozin Studies

SGLT 2 Inhibitors: Questions to be addressed

- Durability: Does the efficacy of SGLT2 inhibition wane once blood glucose falls into the normal range?
- Safety and tolerability: What is the long-term safety of this class? Does the risk of nocturia and genitourinary infections limit use in some patients?
- Renal impairment: Is SGLT2 inhibition effective in patients with renal impairment?

Case Presentation
Karen

- 45-year-old Caucasian woman with a 2-year history of type 2 diabetes mellitus; initial A1c = 8.5 %
- Started on metformin, increased to a dose of 1000 mg twice daily. A1c with level to approx. 7.5 % at 12 months
- 1.5 years after diagnosis, A1c = 7.8 % and glipizide 10 mg daily was added to her treatment regimen; had experienced a weight gain of 5 pounds as well as several episodes of mild hypoglycemia over the next 6 months, she discontinued sulfonylureas
Case Presentation
Karen

- Currently working as Administrative Ass’t, walks 3-5 days a week, 30 minutes per day
- States diet isn’t great, because she’s “human”; but feels she does as well as she can. Tries to prepare meals at home at night; for lunch, has to grab something “quick, and not always ideal”
- She has heard about injections for weight loss, not excited about injecting but will try if it will help
- She also is concerned about the complications and knows her A1c needs to be lower

Two years after diagnosis, and on metformin only, A1c = 7.9 %

SMBG: her fasting plasma glucose (FPG) averages 140 mg/dL and her postprandial glucose (PPG) ranges from 190-235 mg/dL.

5 feet 4 inches tall (body mass index [BMI] = 36 kg/m^2)

Blood pressure is 135/84 mmHg; and her lipids are within the target range according to laboratory tests performed last week

Which of the following statements is most likely correct with regard to treatment considerations for this patient?

1. Her lack of more exercise is the most likely contributing factor to her weight gain
2. She should be counseled to adhere to her glipizide treatment because metformin is more likely to contribute to her weight gain than glipizide
3. A positive energy balance and her glipizide treatment are the most likely contributing factors to her weight gain
4. It was prudent for her to stop taking the sulfonylurea

What is your A1C glycemic goal for this patient?

1. <7.5
2. <7.0
3. <6.5
4. Lowest possible without hypoglycemia

My add-on drug to metformin for management of hyperglycemia in this patient is:

1. Another trial of Sulfonylurea (lower dose) or glinide
2. TZD
3. SGLT 2 inhibitor (if available)
4. DPP-4 inhibitor
5. GLP-1 analog
6. Alpha-glucosidase inhibitor
7. Colesevelam
8. Insulin

If this patient were 65 years old instead of 45 yo, and has had diabetes for 20 years, my A1c goal for this patient would be:

1. < 8
2. < 7.5
3. < 7
4. < 6.5
5. Lowest possible without hypoglycemia
If this patient were 65 years old instead of 45 yo, and has had diabetes for 20 years, my add-on drug to metformin for management of hyperglycemia would be:

1. Sulfonylurea or glinide
2. TZD
3. SGLT 2 inhibitor (if available)
4. DPP-4 inhibitor
5. GLP-1 analog
6. Alpha-glucosidase inhibitor
7. Colesevelam
8. Insulin
9. No add-on drug

Question #1  ? POST

- I am ______ in my understanding of the role of the kidney in glucose regulation.
  1. Very Confident
  2. Confident
  3. Somewhat Confident
  4. Unsure/Not Confident

Question #2  ? POST

- _____ actively transports most of the glucose across the proximal convoluted tubule cells of the kidney.
  1. SGLT 1
  2. SGLT 2
  3. GLUT 1
  4. GLUT 2

Question #3  ? POST

- I am ______ in my understanding of newer therapies that do not specifically target insulin resistance and impaired insulin secretion in type 2 diabetes
  1. Very Confident
  2. Confident
  3. Somewhat Confident
  4. Unsure/Not Confident

Question #4  ? POST

- Potential benefits of the SGLT2 inhibitors in addition to glucose lowering include:
  1. BP lowering
  2. Reduction in LDL-C
  3. Weight loss
  4. BP lowering and weight loss
  5. All of the above

Question #5  ? POST

- If available, I would most likely use SGLT 2 inhibitors ______ in some of my type 2 diabetes patients.
  1. As monotherapy
  2. In combination with other antidiabetic agents (not including insulin)
  3. In combination with insulin
  4. 1 and 2
  5. 1 and 3
  6. 1, 2, and 3
  7. I am unsure
  8. I would not use them