Unmet Challenges in Diabetes

Edward C. Chao, DO
Associate Clinical Professor of Medicine
University of California, San Diego
VA San Diego
Disclosures

- Advisory Board - Janssen
A Question:

- What can we do differently on Monday that can help our pts living with diabetes?
Our Road Map

• What are the challenges for patients living with DM?

• What are the newest medications?

• What’s in the pipeline for future therapeutic options?

• What’s the latest on the microbiome and DM?

• What are some practical strategies to assist our patients?
A Case

- 57-year-old African-American male dx with T2DM in 2006; home BS “always high, in the 200s or more”, did not bring log book or glucometer
- No microvascular or macrovascular complications
- Meds include: Metformin SA 2000 mg qday, Glipizide SA 10 mg qday, Atorvastatin 40 mg QHS
- FH: +T2DM and CAD in father and sister
- PE: Wt 99.8 kg (220 lb), BMI 37, BP 142/88
- Labs: 1/3/17: A1c: 12.7% peak: 2/25/16: 14.1%
- Very hesitant to take injectable medication; asks for “more time to get back on track”
Look familiar?
“Diabetes is a whole-body disease. It illustrates the osteopathic philosophy that the body is a unit—it’s very unusual to see a diabetes patient who doesn’t have any other diagnoses.”

- Randy Shuck, DO
What are some challenges for patients living with DM?
Despite our advances...

Age-adjusted Percentage of US Adults With Diagnosed Diabetes

1994

2000

2010

 Centers for Disease Control and Prevention. Available at:
Republished with permission.
Diabetes in the US

1 out of 9 adults have DM

29.1 million adults have DM

1 OUT OF 4 do not know they have diabetes

By 2050: 1 out of 3 adults

Every 23 seconds, someone in the US is dx with DM

In the US, diabetes accounts for, on average:

- Up to 1 case of blindness every 22 minutes
- 1 case of kidney failure every 10 minutes
- 1 lower limb amputation every 7 minutes

Worldwide, 1 person dies every 6 seconds from diabetes and its complications

That’s more than 14,000 people a day

*Type 1 or Type 2 diabetes.
ONLY ABOUT HALF OF PATIENTS ACHIEVE HbA1c <7% WITH VIRTUALLY NO CHANGE OVER THE LAST DECADE

NHANES Data

<table>
<thead>
<tr>
<th>Year</th>
<th>% of Patients Achieving HbA1c &lt;7%</th>
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<tbody>
<tr>
<td>2003-2006</td>
<td>56.8%</td>
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<tr>
<td>N=999</td>
<td></td>
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<tr>
<td>2007-2010</td>
<td>52.2%</td>
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<tr>
<td>N=1444</td>
<td></td>
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<tr>
<td>2011-2014</td>
<td>50.9%</td>
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<tr>
<td>N=2677</td>
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NHANES, National Health and Nutrition Examination Survey.

aPatients with either Type 1 or Type 2 diabetes.

What are some challenges of T2DM management?

At the time of dx T2DM:

» 50% of patients already have complications
» At least 50% of β-cell function has already been lost

- Multivariate etiopathology
- Different factors to different degrees
- Clinical inertia - both patients and HCPs
- No log book, lost-to-f/u, adherence
- Side effects:
  – Hypoglycemia: Insulin, sulfonylureas (SFU)
  – Weight gain: Insulin, SFU, thiazolidinediones (TZD)
Medications: GLP-1 Receptor Agonists
Incretins (INtesinal seCRETion of INsulin):

• Gut hormones that stimulate glucose-dependent insulin secretion

• GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide): the best characterized incretins

• Unlike GIP, GLP-1 potently stimulates insulin secretion and reduces blood glucose in patients with type-2 diabetes
The Incretin Effect

Oral glucose elicits a greater insulin response than IV glucose (the “incretin effect”)

*P < 0.05.
The Incretin Effect is Diminished in Type 2 Diabetes


*P < 0.05.*
GLP-1 Modulates Numerous Functions in Humans

- **Stomach:** Helps regulate gastric emptying
- **Liver:**
  - Glucagon reduces hepatic glucose output
  - Postprandial glucagon secretion
- **Beta cells:** Enhances glucose-dependent insulin secretion
- **Alpha cells:**
  - Postprandial glucagon secretion

GLP-1: Secreted upon the ingestion of food

Promotes satiety and reduces appetite

Incretin Secretion and Metabolism

Active Incretins (GLP-1)

DPP-IV

GLP-1

Meal

Inactive Incretins

Renal Clearance

Incretin Actions
Incretins:

- But: native GLP-1: very brief half-life: 1-2 min

- DPP-4 (Dipeptidyl peptidase-4) enzyme rapidly degrades GLP-1

- 2 strategies:
  - 1) Develop GLP-1 RAs (receptor agonists) that mimic GLP-1, are resistant to DPP-4 or:
  - 2) Inhibit DPP-4 - extend GLP-1 half-life

- Mimic action of GLP-1, increase incretin effect, stimulate insulin release
- SQ
GLP-1 RA

- Exenatide (Byetta), BID
- Exenatide ER (Bydureon), q wk
- Liraglutide (Victoza), qday
- Albiglutide (Tanzeum), q wk
- Dulaglutide (Trulicity), q wk
- Semaglutide PO
## GLP-1 RA

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<td><strong>A1c</strong></td>
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<tr>
<td><strong>Wt Loss</strong></td>
<td>-1 to -4 kg</td>
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</table>
| **BP** | SBP -1 to -7 mm/Hg  
          DBP: similar to placebo |
| **Benefits** | Weight loss  
                  Low incidence of hypos |
| **Adverse Effects** | N/V  
                       Diarrhea  
                       URI  
                       Injection site rxns |
Some reports, but no evidence for a causal relationship between these agents and acute pancreatitis in humans.

(FDA review of studies in > 80,000 pts: no evidence of increased risk of pancreatitis or pancreatic ca with incretins)

- D/c immediately in patients developing acute pancreatitis
- Use with caution in pts at risk for pancreatitis
- Medullary thyroid ca - not in humans
DPP-4 Inhibitors

- PO

- Provide a physiological increase in GLP-1 levels - by inhibiting the DPP-4

- Renal dose-adjustment if CKD (except linagliptin)
Incretin Secretion and Metabolism

Meal

Active Incretins (GLP-1)

DPP-IV Inhibitors

DPP-IV

GLP-1 RA

Incretin Actions

Inactive Incretins

Renal Clearance
DPP-4 Inhibitors

- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)
- Alogliptin (Nesina)
DPP-4 Inhibitors: Safety

• Severe joint pains (33 patients - 2006-2013)

• Heart failure - Saxaglipitin
## GLP-1 RA vs DPP-4 Inhibitors

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<td>N/V Diarrhea</td>
<td>Nasopharyngitis HA URI</td>
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<tr>
<td><strong>+ and -</strong></td>
<td>Better glycemic control and wt loss</td>
<td>Less frequent nausea vs GLP-1 RA, PO admin</td>
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SGLT2 Inhibitors
2nd century AD: Aretaeus of Cappadocia: polyuria is a compensatory mechanism in patients with diabetes

His conclusion: DM was due to a fault in the kidneys

The kidney’s involvement in glucose homeostasis: first described in the 1930s

The kidney was thought to be a source of glucose only after prolonged fasting or under acidic conditions

Plasma glucose is kept in a narrow range (~70-100mg/dL) in part by:

1. Glucose uptake: (~25-35 g/day, kidneys use ~10% of all the glucose used by the body)

2. Gluconeogenesis: ~15-55 g/day

3. Glucose reabsorption: ~180 g/day

Glucose is a polar compound to which lipid-rich cell membranes are impermeable.

Movement across cell membranes thus requires assistance: carrier proteins.

2 classes of glucose transporters:
- Sodium-linked glucose transporters (SGLT)
- Facilitative glucose transporters (GLUT)

Glucose Transport in PCT Epithelial Cells

SGLT2
High capacity
Low affinity

SGLT1
Low capacity
High affinity

Renal Threshold for Glucose Excretion

RT = renal threshold.
Inhibiting SGLT2 Promotes Urinary Glucose Excretion

- SGLT2 inhibitors lower the threshold at which glucose is excreted, leading to
  - Increased urinary glucose excretion
  - Decreased return of glucose to circulation
  - Decreased blood glucose levels

RT = renal threshold.
Glucosuria: A Paradigm Shift

• Increased glucose reabsorption in individuals with DM - an adaptation gone wild

• Glucosuria - has been regarded as marker of diabetes

• Interesting change in perspective: Viewing this as a mechanism of action for treatment
SGLT-2 Inhibitors

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
## SGLT-2 Inhibitors

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# SGLT-2 Inhibitors

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<th><strong>Dose Range</strong></th>
<th>• Only use if the eGFR is &gt; 45 cc/min</th>
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| **Benefits**   | • No hypoglycemia (unless when being used with SFU or insulin)  
• Mean A1C reduction approximately 1% (starting from a baseline A1c of ~8.0%)  
• Weight loss (2-5%) and systolic BP reduction (2-6mmHg) |
| **Concerns**   | • Genital mycotic infections. In women (6 to 12% higher than comparator) and in uncircumcised males (2 to 6% higher than comparator)  
• Hypotension secondary to volume contracture esp. in the elderly, those on loop diuretic use and in patients reduced renal function.  
• Urosepsis  
• Diabetic ketoacidosis  
• Bone fractures (Canaglifozin) |
| **Clinical Pearls** | First oral diabetes medication that leads to statistically significant weight loss. |
# Summary

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MAKE THE GRADE IN DIABETES CONTROL

- BLOOD SUGAR CONTROL
- TAKING MEDICATION AS DIRECTED
- DIABETES EDUCATION

www.gradestudy.com
Cardiovascular Outcomes
Cardiovascular

• Diabetes: A cardiovascular disease presenting as a metabolic disorder

• FDA 2008: required long-term cardiovascular safety data for new diabetes medications

• 3 medications
Empagliflozin Reduces CV Events & Mortality in High-Risk Type 2 Diabetes

**Primary composite endpoint:**
Death from CV causes, nonfatal MI, or nonfatal stroke

- **Placebo** (n=2,333)
  - Base: 12.1%
  - Empagliflozin: 10.5%
  - **RRR=14%**
  - HR=0.86 (0.74-0.99)
  - \( P<0.001 \) for noninferiority
  - \( P=0.04 \) for superiority

- **Empagliflozin** (n=4,687)
  - Base: 14.3%
  - Empagliflozin: 12.8%
  - **RRR=11%**
  - HR=0.89 (0.78-1.01)
  - \( P<0.001 \) for noninferiority
  - \( P=0.08 \) for superiority

CV=cardiovascular; MI=myocardial infarction; RRR=relative risk reduction; UA=unstable angina

Lower All-Cause & CV Mortality With Empagliflozin Vs Placebo in High-Risk Patients

EMPA-REG OUTCOME

Placebo (n=2,333)  Empagliflozin (n=4,687)

Death from any cause

% Subjects

RRR=32%

Death from CV causes

% Subjects

RRR=38%

HR=0.68 (0.57-0.82)  HR=0.62 (0.49-0.77)

P<0.001  P<0.001

39 patients would need to be treated over 3 years to prevent 1 death

CV=cardiovascular; MI=myocardial infarction; RRR=relative risk reduction

Lower Heart Failure Hospitalization With Empagliflozin Vs Placebo in High-Risk Patients

EMPAR-REG OUTCOME

Placebo (n=2,333)  Empagliflozin (n=4,687)

Heart failure hospitalization

RRR=35%

4.1%  2.7%

HR=0.65 (0.50-0.85)

P=0.002


RRR=relative risk reduction
LEADER Study - Liraglutide

What’s in the pipeline?
Bionic (Artificial) Pancreas

**HOW THE DEVICE WORKS**

1. Sensor monitors blood sugar levels
2. Readings transmitted to control device where correct dose is calculated
3. Insulin pump injects dose into skin
An Implantable Device
What’s the latest on the microbiome and DM?
The Microbiome

“All disease begins in the gut.”
- Hippocrates
The Microbiome
Staggering Numbers

- Symbiotic and pathogenic bacteria, viruses, fungi that share our space
- 100 trillion bacteria, 10 trillion human cells (10:1)
- 2014: 3:1 (37 trillion human)
- 2016: nearly even: 40 trillion bacteria, 30 trillion human
- Microbes: 250-800 times more genes vs human
Questions

• Balance altered - processed foods, antibiotics, indoor plumbing

• Differences - composition of gut microbes in those with DM and those without

• Chicken/Egg: Does DM alter the microbiome? Or does the microbiome facilitate developing DM?
Study

• Men with metabolic syndrome - gut lavage

• Fecal infusions from: 1) lean donors or 2) themselves

• Recipients from lean: increased insulin sensitivity after 6 wks, 2.5-fold increase in beneficial bacteria

• Decreased over time

• Wide inter-individual variability

Future studies

- Protocol for double-blind, placebo-controlled randomized study of a probiotic

- 60 adults with BMI ≥ 25 kg/m², pre-DM or T2DM

- Primary outcome: change in FPG over 12 weeks

What are some strategies that can help our pts?
Incidence of Diabetes

The DPP Research Group, *NEJM* 346:393-403, 2002
• "What’s bothering you most about your diabetes?" And listen!

• It’s not non-compliance!

• It takes a village

• Analogies - the car or another

• Build momentum: invite the pt to select 1 change - start a success cycle
Takeaways

• New medication: changing how we view glucosuria

• ?future therapeutics – looking within

• Multiple ways to help pts and families - It’s a marathon
“To find health should be the object of the doctor. Anyone can find disease.

- Andrew Taylor Still, DO
Thank you!

ecchao@ucsd.edu

OPSC