Pumps, Sensors & Meds, Oh My!
New Treatments for Type 1 & Type 2 Diabetes

Community Medical School
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In Memory

Angel Elizabeth Dudley
June 21, 1961 - October 16, 2018
Outline for Tonight’s Talk

• Review the prevalence of diabetes in the U.S. and around the world
• Discuss the cost of the current diabetes epidemic
• Investigate new treatments and technologies for patients with diabetes
• How can you take better care of your diabetes?
The Current State of Diabetes
Prevalence of Diabetes in the U.S.-2017 Data

- 30.2 million (12.2% of the adult population) in the U.S. have diabetes
- Another 7.2 million are undiagnosed
- 34% of adults in the U.S. have prediabetes
- 25% of adults in the U.S. over the age of 65 have diabetes and 48% have prediabetes
Prevalence of Diabetes in U.S. in 1994

- <4.5%
- 4.5-5.9%
- 6.0-7.4%
Prevalence of Diabetes in U.S. in 2015

- 6.0-7.4%
- 7.5-8.9%
- >9.0%
The Challenge

30.2 Million with Diabetes
Worldwide Prevalence of Diabetes

Economic Cost of Diabetes in the U.S.

Economic Costs of Diabetes in the U.S. in 2017

Diabetes Care Volume 41, May 2018

American Diabetes Association

American Diabetes Association. Diabetes Care, 2018;41:917-928
Economic Cost of Diabetes in the U.S.

- $327 billion were spent in 2017 on patients with diabetes
  - $237 billion in direct medical costs and $90 billion in reduced productivity
- Direct medical costs represent a 26% increase since 2012
- More than 300 million work days are lost to the economy due to diabetes
- Diabetes resulted in 277,000 premature deaths in 2017

American Diabetes Association. *Diabetes Care*, 2018;41:917-928
Economic Cost of Diabetes in the U.S.

- Medications directly used to treat diabetes = $31 billion
- $15 billion of which is for insulin
  - Increase of 45% over the last 5 year
- 1 in every 4 health care dollars spent was for the care of people with the diagnosis of diabetes
- 1 of every 7 health care dollars can be attributed directly to the care of diabetes

American Diabetes Association. *Diabetes Care*, 2018;41:917-928
DEATHS DUE TO DIABETES COMPLICATIONS CONTINUE AT ALARMING RATE

IN THE US, DIABETES\(^a\) CONTRIBUTES TO, ON AVERAGE\(^1\):  

- 1 stroke every 2 minutes  
- 1 case of ischemic heart disease every 80 seconds  
- 1 case of kidney failure every 10 minutes  
- 1 lower limb amputation every 5 minutes  

DIABETES CONTRIBUTES TO THE DEATH OF 1 PERSON EVERY 2 MINUTES IN THE UNITED STATES

That's more than 768 people a day

OPIOID OVERDOSE CRISIS IN THE UNITED STATES, IN 2016, 1 PERSON DIES EVERY 52 MINS. FROM OPIOID OVERDOSE\(^3\)

That's more than 46 people a day

\(^a\)Type 1 or Type 2 diabetes.  
How do we prevent complications of diabetes?

- **HbA$_1c$ 7.9% vs. 7.0%**

- Risk Reduction:
  - Any Diabetes Related Endpoint: -12% p = 0.029
  - Microvascular Endpoints: -25% p = 0.009
  - Laser Rx: -29% p = 0.003
  - Microalbuminuria (Microalb.): -34% p < 0.001
  - Myocardial Infarction: -16% p = 0.052

Preventing Complications

- Retinopathy
- Nephropathy
- Neuropathy
- Microalbuminuria

Patients with type 1 diabetes (n=1,441)
Adapted from DCCT. Diabetes 1995;44:903-43.
How do we prevent complications of diabetes?

BP 154/87 vs. 144/82 mm Hg

- Any Diabetes Related Endpoint: -24%, p=.0046
- Microvascular Endpoints: -37%, p=.0092
- Retinopathy Progress: -34%, p=.0038
- Stroke: -44%, p=.013
- Heart Failure: -56%, p=.0043

Preventing Complications
How are we doing?

How are we doing?

Drug Development for Diabetes 1950-Present

- Insulin
- SUs - Glipizide, Glyburide, Glimepiride
- SGLT-2 Inhibitors
- Bromocriptine/Colesevelam
- DPP-4 Inhibitors
- GLP-1 Receptor Agonists
- Pramlintide
- Repaglinide, Nateglinide
- Thiazolidinediones
- α-glucosidase inhibitors
- Metformin

Timeline:

- 1950
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010
- 2020
MORE THAN 40 T2DM TREATMENT OPTIONS HAVE BEEN APPROVED SINCE 2005

A New(ish) Approach to Treatment of Type 2 diabetes
Cardiovascular Safety of Diabetes Medications
Contemporary Cardiovascular Outcome Trials (CVOT) in Diabetes
Biology of Incretin Hormones

- Concept that “factors” from the intestine stimulate the endocrine pancreas is not new.\(^1\)
- The term “incretin” arrived in the 1930’s.\(^2\)
- Development of the radioimmunoassay confirmed the “communication” between the intestine and endocrine pancreas.

\(^1\) Bayliss WM, Starling EH. *Proc R Soc Lond Bio* 1902;69:352-353
\(^2\) La Barre J. *Bull Acad R Med Belg* 1932;12:620-634
Biology of Incretin Hormones

L-Cell
- Proglucagon
  - GLP-1 [7-37]
- GIP [1-42]

K-Cell
- ProGIP
  - GIP [1-42]

DPP-4
- INACTIVE
- ACTIVE
Biology of Incretin Hormones

• “Incretin effect”
• May account for 50-70% of total insulin secreted after a meal
• Incretins are hormones that enhance glucose-stimulated insulin secretion

![Graph showing insulin levels after intravenous and oral glucose consumption] (Nauck M, et al. Diabetologia 1986;29:46-52)
Reduced Incretin Effect

**Control Subjects**

- Intravenous Glucose
- Oral Glucose

**Patients with T2DM**

Incretin Therapies

- Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase-4 inhibitors (DPP-4i)
- DPP-4i block the breakdown of GLP-1 and GIP in the body
- GLP-1 RA mimic the action of human GLP-1, but are not easily broken down by natural DPP-4 found in the gut.
Structure of GLP-1 Medications

- **Native human GLP-1**: 97% amino acid homology to human GLP-1

- **Liraglutide**: 53% amino acid homology to human GLP-1

- **Exenatide**: 53% amino acid homology to human GLP-1
GLP-1 Receptor Agonists

GLP-1 RA

Short-acting (<24 hours)
- Exenatide BID
- Lixisenatide Daily

Long-acting (≥24 hours)
- Liraglutide Daily
- Exenatide Weekly
- Albiglutide Weekly
- Dulaglutide Weekly
- Semaglutide Weekly
GLP-1 RA Clinical Characteristics

- Injectable medications (twice daily, daily, weekly)
- Lower A1c by 1-1.5%
- Promote weight loss (3-5 kg)
- Nausea is a common side effect of this class of medication
- Low rates of hypoglycemia
LEADER Trial

- Cardiovascular effect of liraglutide in patients with T2DM
- Double-blind, randomized control trial of liraglutide vs. placebo
- Patients with high CV risk (CAD, CVA, PVD, CHF or CKD)

- Total of 9340 patients were randomized
- Mean follow-up was 3.8 years
- Primary composite outcome was comprised of CV death, nonfatal MI and nonfatal stroke

LEADER Trial

A Primary Outcome

Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority

Placebo
Liraglutide

Patients with an Event (%)

0 5 10 15 20
0 10 20 30 40 50 60 70 80 90 100

No. at Risk

Months since Randomization

Liraglutide
4668 4593 4496 4400 4280 4172 4072 3982 1562 424

Placebo
4672 4588 4473 4352 4237 4123 4010 3914 1543 407

Marso SP, et al. NEJM. 2016;375:311-322
SUSTAIN-6 Trial

A Primary Outcome

- Hazard ratio, 0.74 (95% CI, 0.58–0.95)
- P<0.001 for noninferiority
- P=0.02 for superiority

No. at Risk
- Placebo: 1649, 1616, 1586, 1567, 1534, 1508, 1479
- Semaglutide: 1648, 1619, 1601, 1584, 1568, 1543, 1524

SGLT-2 Inhibitors

- Newer class of medications
- Block the reabsorption of glucose by the kidney
- Low risk of hypoglycemia
- Weight loss
- Increase risk of infections and dehydration from increased urine output
How do SGLT-2 Inhibitors Work?

The Newest Antihyperglycemic Class

*SGLT2 Inhibitors*

SGLT2 inhibitors suppress the action of SGLT2

Glucose

SGLT2 inhibitor

Lost in urine

Increase urinary glucose excretion

Reduce glucose reabsorption

EMPA-REG OUTCOM Trial

A Primary Outcome

Patients with Event (%)
0 5 10 15 20

Month
0 6 12 18 24 30 36 42 48

Placebo
Empagliflozin

Hazard ratio, 0.86 (95.02% CI, 0.74–0.99) P=0.04 for superiority

No. at Risk
Empagliflozin 4687 4580 4455 4328 3851 2821 2359 1534 370
Placebo 2333 2256 2194 2112 1875 1380 1161 741 166

Zinman B, et al. NEJM. 2015
CANVAS PROGRAM

A Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke

Hazard ratio, 0.86 (95% CI, 0.75–0.97)  
P<0.001 for noninferiority  
P=0.02 for superiority

No. at Risk
Placebo 4347 4239 4153 4061 2942 1626 1240 1217 1187 1156 1120 1095 789 216  
Canagliflozin 5795 5672 5566 5447 4343 2984 2555 2513 2460 2419 2363 2311 1661 448

Neal B, et al. NEJM. 2017;377:644
2018 ADA/EASD Consensus Guidelines

**First-Line Therapy is Metformin and Comprehensive Lifestyle (Including Weight Management and Physical Activity)**

- If HbA1c above target, proceed as below.

### Established ASCVD or CKD

**EITHER/OR**

- GLP-1RA with proven CVD benefit
- SGLT-2i with proven CVD benefit

**IF HbA1c above target**

- If further intensification is required or patient is new, unable to tolerate GLP-1RA and/or SGLT-2i, choose agents demonstrating CV safety:
  - Consider adding the other class (GLP-1RA and/or SGLT-2i) with proven CVD benefit
  - DBP-4 if not on GLP-1RA
  - Basal insulin
  - TZD
  - SU

### HF or CKD predominates

**PREFERRABLY**

- GLP-1RA with evidence of reducing HF and/or CKD progression in CVOT if already tolerated

**IF HbA1c above target**

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety
  - Consider adding the other class with proven CVD benefit
  - DBP-4 if not already in the setting of HF or on GLP-1RA
  - Basal insulin
  - SU

### Without established ASCVD or CKD

**IF HbA1c above target**

- Continue with addition of other agents as outlined above

- Consider the addition of SU or basal insulin
  - Choose 1st generation SU with lower risk of hypoglycemia
  - Consider basal insulin with lower risk of hypoglycemia

- SGLT-2i

**Compelling need to minimize hypoglycemia**

- GLP-1RA
- SGLT-2i
- TZD

**Compelling need to minimize weight gain or promote weight loss**

- GLP-1RA with good efficacy for weight loss

**Cost is a major issue**

- Insulin therapy: basal insulin with lowest acquisition cost
- Consider DBP-4 or SGLT-2i with lowest acquisition cost
New Technologies for the Treatment of Diabetes
New Technologies for the Treatment of Diabetes
DEXCOM G6 Continuous Glucose Monitor® (CGM)
DEXCOM G6 Continuous Glucose Monitor® (CGM)
FreeStyle Libre Flash CGM®
Eversense®
New Technologies for the Treatment of Diabetes
Medtronic 670G® Closed Loop Insulin Pump
Artificial Pancreas
What Can You Do to Help Reduce Your Risk
What can you do help?

- See your doctor regularly (Every 3-6 months)
- See your dentist regularly (Every 3-6 months)
- See your eye provider for **dilated** eye exam (Annually)
- Exercise on a regular basis and lose weight if you need to (5-7%)
- Work on your diet (CDE or CDE/RD or RD)
What can you do help?

- Obtain urine test to look for early signs of kidney damage (microalbuminuria)
- Check your blood pressure on a regular basis using a home blood pressure monitor
- Get your cholesterol level checked
- **Take your medication**
- Stay informed regarding new treatments
- Ask your provider if there are any new treatments or technologies that might benefit you
What can you do to help?
Conclusions

• Diabetes is a world-wide epidemic
• Significant financial and human costs
• Newer treatments are changing the everyday life of people with diabetes
• Newer treatments are providing additional benefits than lowering blood sugars
• Stay up to date and ask your provider regarding new treatments or technologies
• Take care of yourself!
Improvements in clinical trials is not translating to the real world

The efficacy gap between clinical trial and real-world results

**GLP-1 RA (12 months)**
- N=2600 (8.4%)
- N=221 (-0.52%)

**DPP-4i (12 months)**
- N=1889 (7.8%)
- N=652 (-0.51%)

**Baseline HbA1c**
- 8.3% (GLP-1 RA), 8.2% (DPP-4i)

**Change in HbA1c (%):**
- 8.4% to 8.3% (GLP-1 RA)
- 7.8% to 8.2% (DPP-4i)

**GAP**
- -1.25%
- -0.68%

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*a* Identified 11 pivotal randomized controlled trials with published change in HbA1c (7 GLP-1 RA [2600 patients] and 4 DPP-4i [1889 patients]).

*b* Optum/Humedica SmartFile database (2007-2014) was used (GLP-1 RA 221 patients; DPP-4i 652 patients). Change in HbA1c measured from drug initiation to 365±90 days later. Carls GS et al. 76th ADA Scientific Sessions. June 10–14, 2016. Poster 117-LB.
Adherence rates for oral agents are less than 50%

PDC, proportion of days covered; SU, sulfonylurea; TZD, thiazolidinedione. A retrospective claims analysis of 238,372 patients with T2D with at least 1 prescription claim for a DPP-4i, SU, or TZD from January 1, 2009 to January 31, 2012. Adherence defined as PDC ≥0.8. Farr AM et al. Adv Ther. 2014;31:1287-1305.
Poor adherence is the key contributor to the efficacy gap

GLP-1 RA adherence rate in Real World = 29%

RCT, randomized clinical trial.

a Linear regression model fitted to estimate the change in HbA1c 1 year after initiating GLP-1 RA or DPP-4i based on baseline and treatment characteristics. b Optum/Humedica SmartFile database (2007-2014) was used (GLP-1 RA 221 patients; DPP-4i 652 patients). Change in HbA1c measured from drug initiation to 365±90 days later. c Medical adherence classified as poorly adherent if percentage of days covered (PDC) <80%. Carls GS et al. 76th ADA Scientific Sessions. June 10–14, 2016. New Orleans, LA. Poster 117-LB.