21st Century Diabetes Management in Primary Care: Better results, Less Stress

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Disclosures

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OUTLINE

• History of Diabetes - from glycosuria to pathophysiology
• Understand pathogenesis of Type 2 Diabetes
• Treat Insulin Resistance
• Current Medication Options - goals and options
• Practice Quality Improvement
History

† 1500 BCE India - “honey urine”

† Ancient Chinese - sugar urine disease

† 250 BC Ancient Greece - Diabetes, Appolonius of Memphis (passes through urine)

† 1674 AD Sir Thomas Willis - Diabetes Mellitus (Sweet Urine)
History

• 1776 Matthew Dobson MD - sugar in urine and blood

• 1889 pancreas in dogs

• 1910 islets of Langerhans. Proposed “Insulin”

• 1921 Banting and Best
History

• 1942 Sulfonylureas (glipizide, glimepiride)

• 1956 Biguanides (phenformin) - *Gallega officinalis* (French lilac)
The Triumvirate: beta cell, muscle, liver: A Collusion responsible for NIDDM
1987 Lilly Lecture, Ralph DeFronzo, MD

Pathogenesis of Type 2 Diabetes

- Impaired insulin secretion
- Pancreas
- Hyperglycemia
- Increased HGP
  - Liver
- Decreased glucose uptake
  - Muscle

Adapted from DeFronzo RA. Diabetes. 1987;36:667-687.
3A. β-Cell-Centric Construct: Egregious Eleven

The β-Cell is the FINAL COMMON DENOMINATOR of β-Cell Damage

8. Colon/Biome
   Abnormal-microbiota; possible decreased
   GLP-1 secretion

9. Immune
   Dysregulation/Inflammation

10. Stomach/Small intestine
    Increased rate of
    glucose absorption

11. Kidney
    Increased glucose re-absorption

1. Pancreatic β-cells
   ↓ β-Cell function
   ↓ β-Cell mass
   ↓ Insulin

FINAL COMMON
DENOMINATOR

2. ↓ Incretin
   effect

3. α-cell
   defect

   ↑ Glucagon

HYPERGLYCEMIA

7. Brain
   Increased appetite
   Decreased morning
   dopamine surge
   Increased sympathetic
   tone

6. Liver
   Increased glucose
   production

5. Muscle
   Decreased
   peripheral muscle
   uptake

4. Adipose
   Increased lipolysis

INSULIN RESISTANCE
Early T2D - Insulin Resistance
A 40 year old male patient with a history of treated hypertension is seen for a check up, with no new complaints. His BP is 135/85, BMI 28. On laboratory exam, his lipid profile includes total cholesterol 216, HDL 32, LDL 135, Triglyceride 255. His A1C is 6.0%. He has a +FH for T2DM in his mother.

Question 1. At this level of glycemia, which of the following statements is the most likely explanation of his elevated glucose?

1. His insulin resistance is high, and his pancreatic Beta Cells are failing to supply insulin.
2. His insulin resistance is high, and his pancreatic Beta cells are producing a normal amount of insulin.
3. His insulin resistance is high, and his pancreatic Beta cells are producing an elevated amount of insulin.
4. His insulin resistance is normal, and his pancreatic Beta cells are failing.
Progressive Nature of Type 2 Diabetes

Prediabetes (Obesity, IFG, IGT)

Diabetes diagnosis

Postmeal Glucose

Fasting glucose

Insulin resistance

Incretin effect

β-cell function

Years

Relative Amount

Glucose (mg/dL)

Diabetes

Macrovascular changes

Microvascular changes

Clinical features

IFG, impaired fasting glucose;
IGT, impaired glucose tolerance.

BETA CELL FUNCTION IN PREDIABETES

• Beta Cell production of insulin decreases in the latter half of Pre Diabetes

• By the time diagnosis T2DM (A1C 6.5%), reduced 50-80%

• But, this is to an extent reversible up to four years after reaching this point.

Insulin Resistance Mechanism

- Level of glycemia = IR adipocyte + IR myocyte + IR hepatocyte - Basal insulin delivery + Bolus insulin delivery

- G. Reaven (1988) IR high across hyperglycemia
  - Regulatory failure of insulin
    - adipocyte - FFA’s not suppressed
    - muscle - glucose uptake low
    - hepatocyte - increased gluconeogenesis
Insulin Resistance results

• Beta cell stress >> de-differentiation >> T2DM
• Hypertension
• Risk of CAD
• Diabetic dyslipidemia (High TG, Low HDL)
• PCOS
• NAFLD

G. Reaven, Diabetes 1988; 37:1595-1607
C Talchi, Cell 2012; 150:1223-1234
INSULIN RESISTANCE PREDIABETES IS NOT A BENIGN CONDITION

- In DPP cohort, 7.9-12.6% had diabetic retinopathy
- There is a 5-10% risk of peripheral neuropathy
- 1.6 X increased risk of Cardiovascular Disease

Prediabetes

- Long-term consequences include
  - Hypertension\(^1\)
  - Cancer\(^2\)
    - Risk increased by 15%
    - Stomach/colorectal, liver, pancreas, breast, endometrium
  - Alzheimer’s disease\(^3\)

Implications of IR for Model of Care

• Cellular damage occurs before glucose at T2D level

• End result injury (ASCVD, neuropathy, retinopathy) may be the presenting symptom, not symptomatic hyperglycemia

• Goal of Diabetes Care - prevent microvascular and microvascular disease

• We will do better at prevention of disease with proactive models of care
Treatment of Early Diabetes

S. Schwartz et al. Dia Care 2016;39:179-186
Question 2. Which of the following describes the best clinical option at this point.

1. Advise him to change his diet and increase physical activity, and schedule him for return in 6 months with repeat A1C.
2. Refer him to an intensive lifestyle change program, with return in 6-12 months.
3. Advise him to change his diet and increase physical activity, begin metformin, and schedule follow up in 6-12 months with lab.
# TREATMENT OF INSULIN RESISTANCE

<table>
<thead>
<tr>
<th>STUDY</th>
<th>INTERVENTION</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Da Qing</td>
<td>lifestyle change</td>
<td>43% reduced Incidence/10 years</td>
</tr>
<tr>
<td>Finnish DPS</td>
<td>lifestyle change</td>
<td>58% reduced incidence/3 years</td>
</tr>
<tr>
<td>DPP</td>
<td>lifestyle change</td>
<td>58% reduced incidence/3 years</td>
</tr>
<tr>
<td>DPP</td>
<td>*metformin</td>
<td>31% reduced incidence/3 years</td>
</tr>
<tr>
<td>DPP</td>
<td>lifestyle change</td>
<td>34% reduced incidence/10 years</td>
</tr>
<tr>
<td>Weight Loss/ NASH</td>
<td>lifestyle change</td>
<td>67% reduced incidence NASH</td>
</tr>
<tr>
<td>NDPP</td>
<td>lifestyle change</td>
<td>4.2% weight loss/.3% per session</td>
</tr>
<tr>
<td>RYGB</td>
<td>*surgery</td>
<td>27% weight loss/12 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51% remission from T2DM</td>
</tr>
</tbody>
</table>
Progressive Nature of Diabetes

• Early Disease: the key is **weight loss** by intensive lifestyle change, to improve blood glucose

• STUDY: Early versus late disease: Very low CAL Diet, measured after 8 weeks.

• Distinguish those with DM <4 years from >8 years

  • >14% weight loss, RESULTING IN...

  • DM < 4 years - 87% Normal fasting glucose

  • DM 8-23 years - 50% Normal fasting glucose

Stevens S. - 2015
TZD in early Disease

• TZD - Troglitazone in DPP, stopped due to liver toxicity
  • Troglit.  3 cases DM/100 patient years
  • Placebo 12 cases DM/100 patient years
  • metformin 6.7 cases DM/100 patient years
  • ILI  5.1 cases DM/100 patient years

Knowles WC, 2005
Pioglitazone in Early Disease

• Multi-center RCT - included 30 minutes diet advice

• Pioglitazone vs placebo

• 2.4 years

• Results: Pioglitazone >>5% conversion to T2D
  • Placebo >>16.7% conversion to T2D
  • 72% decreased conversion

DeFronzo 2011
Metformin Activity in Diabetes

• Still no agreed primary activity of metformin

• 2016 - the primary glucose lowering effect resides in the gut (L cells?)

• Evidence of connection to bile acid - induced GLP-1 secretion

• alteration of micro biome (Akkermansia app) -less inflammatory, decrease post-prandial glucose

• increased glucose utilization in duodenal cells

How many people need treatment for Insulin Resistance with ILI?

BURDEN OF PREDIABETES IN NEW MEXICO 2015

- 634,975 people with Prediabetes in New Mexico
- 121,557 diagnosed PD 2012
- Approximately 500,000 people don’t know they have PD
- **GOAL**: Refer to ILI, avoid T2D or medical treatment

Treat IR of Prediabetes & Early Diabetes
Refer to a lifestyle change program

1. Refer patients to The New Mexico Department of Health Diabetes Prevention and Control Program

   National Diabetes Prevention Program

   505-850-0176

   2018 - will be covered benefits for Medicare

2. Weight Watchers, etc.

3. TASK: Develop Diabetes Self Management Education and Support Programs (DSME/S) for those with T2DM into lifestyle programs

4. TASK: Encourage Commercial Insurance and Medicaid Coverage for Lifestyle Programs
Medication Management

• Goals - control of the primary end-points - A1C, BP, on a statin

• Patient is the primary manager

• Avoid hypoglycemia

• Not to promote obesity
Treatment of Diabetes

3B. β-Cell-Centric Construct: Egregious Eleven
Targeted Treatments for Mediating Pathways of Hyperglycemia

1. Pancreatic β-cells
- ↓ β-Cell function
- ↓ β-Cell mass
- ↓ Insulin
  - Incretins
  - Ranolazine

FINAL COMMON DENOMINATOR

2. ↓ Incretin effect
- Incretins
- Amylin

3. α-cell defect
- Glucagon
- Incretins
- Pramlintide

HYPERGLYCEMIA

4. Adipose
- TZDs
- Metformin

5. Muscle
- TZDs
- Metformin

6. Liver
- Metformin
-TZDs

7. Brain
- Incretins
- Dopamine agonist- QR
- Appetite Suppressants

8. Colon/Biome
- Probiotics
- Incretins
- Metformin

9. Immune Dysregulation/Inflammation
- Incretins
- Anti-Inflammatories
- Immune modulators

10. Stomach/Small intestine
- GLP-1 Agonists
- Pramlintide
- AGI

11. Kidney
- SGLT2 inhibitors

INSULIN RESISTANCE
Newer Classes of Medications for Diabetes Type 2 Added Since 1995

- 1995  alpha glucosidase inhibitors - Acarbose
- 1995  biguanides - metformin
- 1997  meglitinide - Prandin
- 1999  thiazolidendiones - rosiglitazone, pioglitazone
- 2005  amylin mimetics - Symlin
- 2005  GLP-1 agonists - Byetta, Victoza, Trulicity, Tanzeum, (semaglutide)
- 2006  DPP4 Inhibitors - Januvia, Onglyza, Trajenta
- 2013  SGLT2 inhibitors - Invokana, Farxiga, Jardiance
- Multiple new insulin analogues (long, ultra long, rapid, concentrated)
Question #3

He chooses to manage this himself. He returns to your office a year later with an A1C of 9.0%. At this level, which option below is acceptable according to current guidelines?

1. Counsel that he see a certified diabetes educator for a course of lifestyle management, and begin metformin.

2. Lifestyle management and combination metformin and a GLP-1 receptor agonist.

3. Lifestyle management, pioglitazone, and GLP-1 receptor agonist.

4. Lifestyle management, sulfonylurea, and metformin.

5. Either option 2 or 4 is acceptable.
Lifestyle Management is Integral Component of Diabetes Care

### Start with Monotherapy unless:
- A1C is greater than or equal to 9%, consider Dual Therapy.
- A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure B.2).

#### Monotherapy
<table>
<thead>
<tr>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
<td>high</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>neutral/loss</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>Glucose acidosis</td>
</tr>
<tr>
<td>COSTS*</td>
<td>low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors).

#### Dual Therapy
<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonesures</td>
<td>high</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>intermediate</td>
</tr>
<tr>
<td>DPP-4 Inhibitor</td>
<td>intermediate</td>
</tr>
<tr>
<td>GLT2 Inhibitor</td>
<td>high</td>
</tr>
<tr>
<td>GLP-1 Receptor agonist</td>
<td>highest</td>
</tr>
<tr>
<td>Insulin (basal)</td>
<td>high</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors).

#### Triple Therapy
<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonesures</td>
<td>TZD</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>DPP-4-I</td>
</tr>
<tr>
<td>DPP-4 Inhibitor</td>
<td>SU</td>
</tr>
<tr>
<td>GLT2 Inhibitor</td>
<td>DPP-4-I</td>
</tr>
<tr>
<td>GLP-1 Receptor agonist</td>
<td>GLP-1-RA</td>
</tr>
<tr>
<td>Insulin (basal)</td>
<td>Insulin*</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA. (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

#### Combination Injectable Therapy
(See Figure B.2)
Choosing Medications

- Metformin, sulfonylureas, and Pioglitazone are inexpensive
- GLP-1 Agonists work on many cellular sites, promote weight loss
- Pioglitazone reduces fatty acids in liver - NAFLD/NASH
- DPP-4 inhibitors result in .5% A1C reduction, expensive
- SGLT-2 Inhibitors - lower blood pressure 5/2 mmHg, but may increase risk of amputations, ketoacidosis
  - Consider Obesity Treatment - Belviq, Contrave, Qsymia, Saxenda, Xenical - or generic equivalents
Practice Quality Improvement

1. Chronic Disease >>> Chronic Care model

2. Patient Centered Medical Home
   • Run by office staff
   • Consistent contact with all patients

3. Quality Improvement - EMR >> office staff >> capture hidden patients >> address metrics (make more money)
Chronic Care Model

- A proactive delivery system - planned visits, team-based
- Self management Support
- Decision Support - evidence based medicine
- Clinical Information - registries
- Use Community resources- support healthy lifestyle
- Quality Oriented Culture

ADA Standard of Care 2017
Diabetes Self-Management Education and Support: Component of Standard Diabetes Care \(^1,2\)

“…Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications…” \(^1\)
Recognizing the many benefits of DSMES

*If DSMES was a pill, would you prescribe it?*

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**Scorecard: DSMES vs Metformin**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Benefits Rating</th>
<th>Benefits Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DSMES¹</td>
<td>Metformin²,³</td>
</tr>
<tr>
<td>Efficacy</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Hypoglycemia risk</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Weight</td>
<td>Neutral/Loss</td>
<td>Neutral/Loss</td>
</tr>
<tr>
<td>Side effects</td>
<td>None</td>
<td>GI</td>
</tr>
<tr>
<td>Cost</td>
<td>Low/Savings</td>
<td>Low</td>
</tr>
<tr>
<td>Psychosocial benefits</td>
<td>High</td>
<td>N/A</td>
</tr>
</tbody>
</table>


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1. Powers MA. Diabetes Care (2016)
Sorry State of DSMES Utilization

Medicare provides reimbursement for:

- DSMT - first year 10 hours and 2 hours each subsequent year
- MNT – first year 3 hours and 2+ hours each subsequent year

Referrals are required; easy to make

Diabetes Self-Management Education and Support

Maximizing the Benefits

The DSMES Position Statement describes when, what and how to best provide DSMES. Ensure nutrition, education and emotional health needs are met.

Diabetes Care, The Diabetes Educator, Journal of Academy of Nutrition and Dietetics
Comparing Provider Interventions with DSME

- Lack of treatment intensification in the face inadequate control
- **PATIENT CHOICE** accounts for over 1/2 of lack of improvement
- TRIAD Study - Provider intensification improved A1C .49%
- DROPA1C Study - registry and CDE case management improved A1C 1.5%
- DSME with an educator improved A1C .8% proportional to time with the educator (Norris)
- Nurse/Pharmacist management reduced A1C 3x usual care (Davidson)
Summary – Maximize the Benefits of DSMES

- There are many evidence-based benefits of DSMES. Of note are the many psychosocial benefits and behavioral improvements.

- DSMES is grossly underutilized.

- The DSMES position statement:
  - Describes the 4 critical times to assess, adjust, provide and refer for education.
  - Provides clear expectations of the focus areas of DSMES at each of the 4 critical times.
  - The checklists in the algorithms provide objective criteria for discussing self-management needs with a patient.
  - Health systems should mobilize to ensure all patients have easy access to DSMES, including nutrition, physical, and emotional health needs.
  - Consider automatic referrals for DSMT and MNT; opt-out versus opt-in.
Patient Centered Medical Home

• Patient Centered - Recognizes that the patient is the manager of her/his life, and is managing the care plan 99.9% of the time

• Medical Home - Enlist all staff to interact with patients to their optimum capacity
Quality Improvement

• From National Academy of Medicine - Crossing the Quality Chasm, March 2001

• Institute for Healthcare Improvement: IHI.org

• Focus on the metrics
  - in T2DM primary metrics are A1C every 3-6 months, BP <= 140/90, Rx for a statin, documented eye exams, yearly UACR
  - Secondary - foot exams, control of T2D, pneumovax
  - prevent morbidity and mortality
  - Earn money, feel better about your practice
Cool New Stuff

• TACT study - chelation reduced secondary CV Disease 40%; only in T2D

• CGM - great tool for reducing variability, avoiding hypoglycemia

• GWAS - genome studies identified >140 sites associated with Diabetes - stay tuned

• Organ metabolomics - PET exhibits heart, kidney, brain not taking up glucose

Resources

1. ADA Standards of Care, 2017, Diabetes Care, V40 Supp1, January 2017, also at diabetes.org/professional.
2. DeFronzo, Diabetes 1988; 667-87, The Triumvirate: B-cell, muscle, liver: a collusion responsible for NIDDM.
3. De Fronzo, Diabetes 2009; 58: 773-95, From the Triumvirate to the Ominous Octet: A new paradigm for the treatment of Type 2 DM.
5. NM State DOH, NM Behavioral Risk Factor Surveillance System 2012-13, found at nmhealth.org, diabetes prevention and control.
8. Eastwood, Diabetes Care 2015; 38(12):2325-32, Association between pre diabetes by three different diagnostic criteria and incident CVD differ in southeast asians and europeans.
10. Rudenski, Diabetes Medicine 1988; 5:36-41, Natural History of pancreatic islet cell B-cell function in type 2 diabetes mellitus studied over six years by homeostasis model assessment.
17. Guanwei L, the Lancet May 2008; 371: 1783-1789, DaQing Study
19. Adams TD, NEJM 2017 Sep 21; 377(12): 1143-53, Weight and metabolic outcomes 12 years after gastric bypass
26. Markus ML, Diabetes Obes Metabolism 2017; 19(9): 1214-1222, Evidence connecting old, new, a regulated glucose-lowering drugs to bile acid induced GLP-1 secretion: a review.
Join nearly 14,000 diabetes professionals like you in helping the American Diabetes Association on the road to a cure for diabetes. Professional Membership provides exclusive, members-only education and resources that benefit you, your patients, and your practice.

*A deeply discounted option for Medicine & Science membership is now available for individuals in emerging nations. Benefits include online access to Diabetes or Diabetes Care, Membership Certificate and USB Card, as well as a listing in our Membership Directory.

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