New Paradigm for the Treatment of Type 2 Diabetes Mellitus

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Introduction (“New Paradigm” is already 8 years old!!)

- Natural History of Type 2 DM
- Chronological History towards development of therapeutic medications
- Modern Principles of DM 2 management
- Patho-physiology driven algorithm
- Prevention of type 2 DM
- Use of technology
Fast Facts about Diabetes

- Diabetes Cost in US healthcare $174 Billion
- 60% on non-traumatic limb amputations
- 44% of all new cases of kidney failure
- 65% of people with DM have nervous system damage (neropathy, depression).
- Diabetic patient are 3 times more likely to die of heart disease
- Common comorbidities: (Hearing impairment, Obstructive sleep apnea, Fatty liver disease, Low testosterone, Periodontal disease, Cancers, Fractures, Cognitive impairment (Hypoglycemia))
Why aren’t patients achieving their goals?

- Although diabetes is incredibly common in the United States, many gaps exist in diabetes management.
- $Cost may be the # ONE limiting factor.
- Clinicians should aim to screen asymptomatic adults aged older than 45 years, as well as adults who are overweight, obese, or have additional risk factor.
- Patient - Physician disconnect
- Isolated Skeptics, Financially Pressured Caregivers, Concerned Seniors, Time Pressured Young Adults.
Criteria for the Diagnosis of Diabetes

- FPG > 126mg/dL
- 2hour PG > 200mg/dL during an OGTT (75gram anhydrous glucola)
- A1C > 6.5%
- Any patient with classic symptoms, and a random glucos > 200mg/dL.
- PRE-Diabetes:
  - FPG> 100 to 125mg/dL
  - 2hour PG from 140 to 199mg/dL
  - A1C > 5.7%
  - (PCO, GestationDM, Obesity)
1. Lifestyle therapy, including medically supervised weight loss, is key to managing type 2 diabetes.

2. Weight loss should be considered as a lifelong goal in all patients with prediabetes and T2D who also have overweight or obesity, utilizing behavioral interventions and weight loss medications as required to achieve chronic therapeutic goals.

3. The A1C target must be individualized.

4. Glycemic control targets include fasting and postprandial glucose.

5. The choice of therapies must be individualized on basis of patient characteristics, impact of net cost to patient, formulary restrictions, personal preferences, etc.

6. Minimizing risk of hypoglycemia is a priority.

7. Minimizing risk of weight gain is a priority.

8. Initial acquisition cost of medications is only a part of the total cost of care which includes monitoring requirements, risk of hypoglycemia, weight gain, safety, etc.

9. This algorithm stratifies choice of therapies based on initial A1C.

10. Combination therapy is usually required and should involve agents with complementary actions.

11. Comprehensive management includes lipid and blood pressure therapies and related comorbidities.

12. Therapy must be evaluated frequently until stable (e.g., every 3 months) and then less often.

13. The therapeutic regimen should be as simple as possible to optimize adherence.

14. This algorithm includes every FDA-approved class of medications for diabetes.
Approach to the management of hyperglycemia

**Patient / Disease Features**

- **Risks potentially associated with hypoglycemia and other drug adverse effects**
  - low
  - high

- **Disease duration**
  - newly diagnosed
  - long-standing

- **Life expectancy**
  - long
  - short

- **Important comorbidities**
  - absent
  - few / mild
  - severe

- **Established vascular complications**
  - absent
  - few / mild
  - severe

- **Patient attitude and expected treatment efforts**
  - highly motivated, adherent, excellent self-care capacities
  - less motivated, nonadherent, poor self-care capacities

- **Resources and support system**
  - readily available
  - limited

**HbA1c 7%**

- **more stringent**
- **less stringent**

**Usually not modifiable**

**Potentially modifiable**
Visualization of glucose variability.

Solid line: a given excursion.
Dashed line: higher glucose variability due to a higher frequency of oscillation.
Dotted line: higher glucose variability due to a larger amplitude.

Note that the mean and area under the curve are identical in the 3 situations.
Diabetes as a Multifactorial Disease

- Genetics/Epigenetics
- Neurobehavioral
- Environment
- Medical
- Immune
- Endocrine
Contribution of Fasting & Post-Prandial Glycemia to A1C in T2DM

Monnier L et al. Diabetes Care 2003; 26: 881
U-shaped morbidity and mortality curve

- Hypoglycemia, Seizure, Death
- Retinopathy, Neuropathy, Nephropathy

Hgb A1c (%)

Relative Risk

Guiding Principles for Diabetes Care

1. Identify Undiagnosed Diabetes & Prediabetes
2. Manage Prediabetes, Prevent Type 2 Diabetes
3. Provide Self-Management Education & Support
4. Provide Individualized Nutrition Therapy
5. Encourage Regular Physical Activity
6. Control Blood Glucose to Prevent or Delay Diabetes
7. Reduce Cardiovascular Disease Risk
8. Detect & Monitor Microvascular Complications
9. Consider Needs of Special Populations
10. Provide Patient-Centered Diabetes Care

National Diabetes Education Program (NDEP)
Natural History of Type 2 Diabetes

- Genes in an ever more stressed environment.
- **Insulin resistance** is at the core of the problem.
- Liver and muscle do not respond appropriately and there is an over production of glucose by the liver in the fasting state.
- This is in spite of elevated insulin levels.
Insulin Resistance: An Underlying Cause of Type 2 Diabetes Mellitus

- Obesity and Inactivity
- Genetic Abnormalities
- Type 2 Diabetes Mellitus
- Hypertension
- Dyslipidemia
- Atherosclerosis
- PCOS
- Medications
- Rare Disorders
- Aging

PCOS = polycystic ovary syndrome.
Natural history of type 2 diabetes

Mean Plasma Insulin During OGTT (μU/ml)

Mean Plasma Glucose During OGTT (mg/dl)

LEAN NGT

OB NGT

OB-IGT

OB-DIAB Hi INS

OB-DIAB Lo INS

Insulin-Mediated Glucose Uptake (mg/m²·min)

Ralph A. DeFronzo Diabetes 2009;58:773-795

©2009 by American Diabetes Association
Insulin resistance in muscle and liver and impaired insulin secretion represent the core defects in type 2 diabetes (1)

Ralph A. DeFronzo Diabetes 2009;58:773-795

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Rollercoaster...

EARLY Intervention...

LATE!
Patho-Physiology; LATE!
**β-Cell Function in Type 2 Diabetes**

Pancreatic function = 50% of normal

HOMA = homeostasis model assessment

Chronological History (Ancient)

- 1552BC Description of polyuria in Egypt.
- 1000BC Sushruta uses the description, “madhumeha” meaning “honey like urine.”
  - He goes on to say that diabetes primarily affects obese people who are sedentary…
  - Tasting of urine to determine presence of diabetes by the sweetness was common.
- 100 AD Aretaeus, (Greek) named "diabetes" from the Greek word for “siphon” or drain off.
  - “it is the greatest of all sufferings, and when a fluid is drunk, it stimulates the discharge of urine. -great masses of the flesh are liquefied”
- 1910 Sir Edward Albert Isolates the Islet
Chronological History (Modern)

1915-1918: Early work with guanidine (Synthalin use stopped in early 1920s)
1922: First exogenous insulin administered to a human
1923: Insulin (Iletin) commercially available in the United States
1935: PZI insulin
1936: NPH insulin
1946: First commercially available SU in the United States
1955: Lente insulins
1956: First recombinant human insulin
1983: Second-generation SUs
1984: Recombinant human insulin
1995: First AGI (acarbose)
1996: First TZD (trogilitazone)
1997: First meglitinide (repaglinide)
2005: First amylin agonist (pramlintide)
2006: First DPP-4 inhibitor (sitagliptin)
2008: Colesevelam approved for diabetes
2009: Bromocriptine approved for diabetes
2013: First SGLT-2 inhibitor (canagliflozin)

John R. White, Jr. Diabetes Spectr 2014;27:82-86

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History of Pharma...
Race to the Moon

- 1982 Oct 28; FDA Approves Lilly's Humulin N
- 1984 May 8; FDA Approves Pfizer's Glucotrol
- 1995 Mar 3; FDA Approves Bristol-Myers Squibb's Glucophage
- 1995 Sep 6; FDA Approves Bayer's Precose
- 1999 May 25; FDA Approves SB Pharmco's Avandia
- 2000 Apr 20; FDA Approves Sanofi Aventis's Lantus
- 2000 May 26; FDA Approves Daiichi Sankyo's Welchol
- 2005 Mar 16; FDA Approves Amylin's Symlin
- 2005 Apr 28; FDA Approves Amylin's Byetta
- 2006 Oct 16; FDA Approves Merck's Januvia
- 2010 Jan 25; FDA Approves Novo Nordisk's Victoza
Treatment Development

• In 1995, the only FDA approved medications for treating type 2 diabetes in the US were sulfonylureas and insulin.
• Newer agents are more costly than the older medications.
• There are now 12 different categories of medications and over 40 different medications aimed at the management of Type 2 diabetes.
• These compounds have been developed during the past 95 years but most in the last 25 years!
• The potential permutations of various combinations of these agents is staggering (over 60) and can be bewildering to the clinicians trying to design the optimum therapy regimen for a given patient.
CHOICES!?!? (WHAT NOW??)

- **Insulins** (Basal, Bolus, lispro, aspart, glulisone, inhaled, regular, NPH, glargine, detemir, degludec, MIXED, U-500)
- **Biguanides** (metformin)
- **Sulfonylureas** second Gen (glipizide, glyburide, glimepiride)
- **Thiazolidinediones** (pioglitizone, rosiglitizone)
- **α-Glucosidase Inhibitors** (acarbose, miglitol)
- **Meglitinides** (nateglinide and rapaglinide)
- **Glucagon-Like Peptide-1 Receptor Agonists** (exenatide (ER), liraglutide, albiglutide, lixisenatide, dulaglutide)
- **DPP-4 Inhibitors** (sitagliptin, saxagliptin, linagliptin, allogliptin)
- **Amylin Agonists** pramlitide (symlin)
- **Dopamine 2 agonists; bromocriptine** (SHORT acting)
- **Bile acid sequestrants; colesvelam**
- **Sodium Glucose Co-Transporter 2 Inhibitors** (canagliflozin, dapafliflozin, empagliflozin)
Patho-Physiology

- Structure dictates function
- Patho-Physiological driven Algorithms
  - Durability
  - Beta Cell Preservation
  - Avoid hypoglycemia
  - Avoid weight gain
Summary of studies examining the effect of sulfonylurea (SU) treatment versus placebo or versus active-comparator on A1C in type 2 diabetic subjects

DURABILITY

Ralph A. DeFronzo Diabetes 2009;58:773-795

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Beta-cell function is better preserved with insulin vs sulfonurea therapy

Michael Alvarsson et al. Dia Care 2003;26:2231-2237
Insulin resistance in muscle and liver and β-cell failure represent the core pathophysiologic defects in type 2 diabetes.

It now is recognized that the β-cell failure occurs much earlier and is more severe than previously thought.

Subjects in the upper tertile of impaired glucose tolerance (IGT) are maximally/near-maximally insulin resistant and have lost over 80% of their β-cell function.

In addition to the muscle, liver, and β-cell (triumvirate), the fat cell (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), α-cell (hyperglucagonemia), kidney (increased glucose reabsorption), and brain (insulin resistance) all play important roles in the development of glucose intolerance in type 2 diabetic individuals. (Ominous Octet)
The ominous octet

Depleted Insulin Secretion

Decreased Incretin Effect

Increased Lipolysis

Islet-α cell

Increased Glucagon Secretion

Increased HGP

Increased Glucose Reabsorption

Decreased Glucose Uptake

Neurotransmitter Dysfunction

Ralph A. DeFronzo Diabetes 2009;58:773-795

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PATHOPHYSIOLOGY

- Beta cell (ROOT CAUSE?)
- Liver (Excess Nutrient)
- Muscle (Lack of movement)
- Adipose (Adiposopathy; Sick Fat Disease)
- Gastointestinal (GLP-1, GIP, Sandostatin)
- Alpha Cell (Glucagon; \( \frac{1}{2} \) the equation)
- Kidney (Nephron; 1,000,000 per kidney)
PathoPhysiology Driven Algorythim

Collectively, the ominous octet dictates:

1) effective treatment of type 2 diabetes will require multiple drugs used in combination will be required to correct the multiple pathophysiological defects,

2) treatment should be based upon reversal of known pathogenic abnormalities and not simply on reducing the A1C, and

3) therapy must be started early to prevent/slow the progressive β-cell failure that already is well established in IGT subjects.
Paradigm Shift...

- A treatment paradigm shift is recommended in which combination therapy is initiated with diet/exercise, metformin (which improves insulin sensitivity and has antiatherogenic effects), a thiazolidinedione (TZD) (which improves insulin sensitivity, preserves β-cell function, and exerts antiatherogenic effects), and exenatide (which preserves β-cell function and promotes weight loss).
- Sulfonylureas are not recommended because, after an initial improvement in glycemic control, they are associated with a progressive rise in A1C and progressive loss of β-cell function.
- Sulfonurea are associated with higher rates of severe hypoglycemia, CVD, and all cause Mortality.
Comparison of the 2009 ADA recommendations (after metformin add a sulfonylurea or insulin) and more modern pathophysiological-based algorithms.

<table>
<thead>
<tr>
<th></th>
<th>ADA</th>
<th>PATHOPHYSIOLOGIC-BASED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durability</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>β Cell Preservation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Ralph A. DeFronzo Diabetes 2009;58:773-795
Current ADA algorithm

- Efficacy, Hypo Risk, Weight, Side effects
- Costs
- A1C greater than 9.0 consider dual therapy
- A1C is greater than 10% BS> 300 or symptoms Combination Injectable therapy
- Metformin PLUS…
- Basal Insulin PLUS, ONE, GLP-1, PreMix
# Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>GLN</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
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<tbody>
<tr>
<td><strong>HYPO</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Neutral</td>
<td></td>
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<tr>
<td><strong>WEIGHT</strong></td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
<td></td>
</tr>
<tr>
<td><strong>RENAL / GU</strong></td>
<td>Contraindicated if eGFR &lt; 30 mL/min/1.73 m²</td>
<td>Exenatide Not Indicated CrCl &lt; 30</td>
<td>Not Indicated for eGFR &lt; 45 mL/min/1.73 m²</td>
<td>Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Effective in Reducing Albuminuria</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>Possible Benefit of Liraglutide</td>
<td>Possible Benefit of Empagliflozin</td>
<td>Genital Mycotic Infections</td>
<td>Neutral</td>
<td>Neutral</td>
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<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<tr>
<td><strong>GI Sx</strong></td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
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<tr>
<td><strong>CHF</strong></td>
<td>Neutral</td>
<td>Possible Benefit of Liraglutide</td>
<td>Possible Benefit of Empagliflozin</td>
<td>Possible Risk for Saxagliptin and Alogliptin</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>More CHF Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More CHF Risk</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>CARDIAC</strong>*</td>
<td>Neutral</td>
<td>Possible CV Benefit</td>
<td>Possible CV Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<td><strong>ASCVD</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
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<td><strong>BONE</strong></td>
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<tr>
<td><strong>KETOACIDOSIS</strong></td>
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</tr>
</tbody>
</table>

- Green: Few adverse events or possible benefits
- Orange: Likelihood of adverse effects
- Yellow: Use with caution
- Black: Moderate to Severe
- Light Yellow: More Hypo Risk
- Red: More CHF Risk
- Blue: Safe
- Green: Benefit
- Brown: Neutral
- Pink: May Reduce Stroke Risk
- Black: Moderate Fracture Risk
- Black: DKA Occurring in T2D in Various Stress Settings

* FDA indication to prevent CVD death in diabetes plus prior CVD events

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### Classes and Mechanism of Action...

**Sensitizers** longer lasting than Secretagogues

<table>
<thead>
<tr>
<th>Mech of Action</th>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitizer</td>
<td>Biguanides</td>
<td>Metformin, Phenformin (W = withdrawn)</td>
</tr>
<tr>
<td>Sensitizer</td>
<td>TZD's (PPAR)</td>
<td>Pioglitizone, Rosiglitizone (?)</td>
</tr>
<tr>
<td>Sensitizer</td>
<td>Dual PPAR agonist</td>
<td>Aleglitizar, Muraglitizar –W</td>
</tr>
<tr>
<td>Secretagogues</td>
<td>Sulfonylurea (K+ATP)</td>
<td>Tolbutamide, glyburide, glipizide, glimepiride</td>
</tr>
<tr>
<td>Secretagogues</td>
<td>Meglitinides (K+ATP)</td>
<td>Nateglinide, repaglinide</td>
</tr>
<tr>
<td>Secretagogues</td>
<td>GLP-1 agonist (CHO DEP)</td>
<td>Exenatide, Liraglutide, Lixisenatide, Albigultide</td>
</tr>
<tr>
<td>Secretagogues</td>
<td>DPP-4 inhibitors</td>
<td>Sitagliptan, Saxagliptan, Linagliptan, Alogliptin</td>
</tr>
<tr>
<td>Analog fast acting insulin</td>
<td>insulin</td>
<td>Lispro, aspart, glulisine, afreeza</td>
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<tr>
<td>Basal Insulin</td>
<td>insulin</td>
<td>Glargine, detimir, degludec</td>
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<tr>
<td>Others</td>
<td>Alpha glucosidase Inhibitor</td>
<td>Acarbose, Miglitol</td>
</tr>
<tr>
<td>Others</td>
<td>Amylin</td>
<td>Pramlintide</td>
</tr>
<tr>
<td>Others</td>
<td>SGLT 2 inhibitor</td>
<td>Canagliflozin, Dapagliflozin, empagliflozin</td>
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<tr>
<td>Others</td>
<td>Ergot Derivative</td>
<td>Bromocriptine mesylate</td>
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<td>Others</td>
<td>Bile acid sequestrant</td>
<td>Cholesevelam</td>
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<tr>
<td>Others</td>
<td>Anorectic (fenfluramine)</td>
<td>Benfluorex, Tolrestat (aldose red -) ; W</td>
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<tr>
<td>Intervention</td>
<td>Hb-A1c decrease</td>
<td>Advantages</td>
</tr>
<tr>
<td>----------------------</td>
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<tr>
<td>Lifestyle Modifications</td>
<td>1-2%</td>
<td>Broad benefits</td>
</tr>
<tr>
<td>Metformin</td>
<td>1-2%</td>
<td>Weight neutral</td>
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<tr>
<td>Sulfonylurea</td>
<td>1-2%</td>
<td>Rapidly effective</td>
</tr>
<tr>
<td>TZD’s</td>
<td>0.5-1.4%</td>
<td>Improved lipid profile, possible decrease in ACS</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>0.5-1%</td>
<td>Weight loss</td>
</tr>
<tr>
<td>α-glucosidase Inhibitor</td>
<td>0.5-0.8%</td>
<td>Weight neutral</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.5-3.5%</td>
<td>Rapidly effective, improved lipid profile</td>
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<tr>
<td>Pramlintide</td>
<td>0.5-1%</td>
<td>Weight loss</td>
</tr>
<tr>
<td>DPP-IV inhibitor</td>
<td>0.5-0.8%</td>
<td>Weight neutral</td>
</tr>
<tr>
<td>Tissue site</td>
<td>Mechanism</td>
<td>Drug</td>
</tr>
<tr>
<td>----------------------</td>
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<tr>
<td>Gastrointestinal tract</td>
<td>Delay of gastric emptying</td>
<td>Pramlintide</td>
</tr>
<tr>
<td></td>
<td>Inhibition of glucagon release</td>
<td></td>
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<tr>
<td></td>
<td>Inhibition of glucose absorption</td>
<td>α-glucosidase inhibitors</td>
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<tr>
<td></td>
<td>Stimulation of GLP-1 release</td>
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<tr>
<td>Pancreatic β cell</td>
<td>Acute stimulation of insulin release</td>
<td>Sulfonylureas</td>
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<tr>
<td></td>
<td>Stimulation of insulin biosynthesis</td>
<td>Meglitinides</td>
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<td></td>
<td>Inhibition of β-cell apoptosis</td>
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<tr>
<td></td>
<td>Stimulation of β-cell differentiation</td>
<td>GLP1/DPP-IV-inhibitors</td>
</tr>
<tr>
<td>Liver</td>
<td>Inhibition of glucose production</td>
<td>Metformin</td>
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<tr>
<td></td>
<td>Increase in hepatic insulin sensitivity</td>
<td></td>
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<tr>
<td>Muscle</td>
<td>Increase in muscle insulin sensitivity</td>
<td>Thiazolidinediones</td>
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<tr>
<td>Adipose tissue</td>
<td>Suppression of NEFA release</td>
<td></td>
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<tr>
<td></td>
<td>Fat redistribution (visceral to subcutaneous)</td>
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<td></td>
<td>Modulation of adipokine release</td>
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</tbody>
</table>
Peptide replacement

- **Insulin Rx**
  - Beta cell rest
  - Glucagon secretion
  - Hepatic glucose output
  - Glucose uptake in muscle
  - Lipolysis in adipose tissue

- **GLP-1RA Rx**
  - Glucose dependent insulin secretion
  - Glucose dependent glucagon secretion
  - Appetite
  - Body weight
  - Insulin sensitivity in muscle
  - Hepatic glucose production
SGLT-2 (Renal Threshold for glucose reabsorption)

**S1 segment proximal tubule:**
~90% of renal glucose reabsorption

**Blood**

**Renal Proximal Tubule**

**Urine**

**Glucose**

**GLUT2**

**Na**

**ATPase**

**Na**

**SGLT-2 inhibitors**

Below RT, minimal glucosuria occurs

Approximate threshold for hypoglycemia ~70 mg/dL

T2DM + CANA RT ~80–100 mg/dL

Healthy RT ~180 mg/dL

T2DM RT ~240 mg/dL

**Plasma glucose (mg/dL)**

**UAE (g/day)**
PREVENTION??

- Is this possible with the epidemic of Type 2 Diabetes spreading like wildfire beneath our watch?
- Metformin therapy for the prevention of Type 2 diabetes should be considered in those with prediabetes, especially for those with BMI > 35, those aged <60 years, women with h/o GDM, and/or those with rising A1C despite lifestyle intervention.
  - (Caution for B12 deficiency)
PREVENTION/DELAY OF TYPE 2 DIABETES

- Patients with IGT, IFG or an A1C of 5.7–6.4% should be referred to an effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 min/week of moderate activity such as walking.
- Follow-up counseling appears to be important for success.
- The chronic treatment of female outbred SHR mice with metformin (100 mg/kg in drinking water) increases life span (increased mean life span by 37.8%) Anisimov, Aging (Albany NY). 2011 February; 3(2): 148–157.
- At least annual monitoring for the development of diabetes in those with prediabetes is suggested.
- Screening for and treatment of modifiable risk factors for CVD is suggested.
GLP-1 for Prevention?

- NOT FDA APPROVED for Prevention
- GLP-1 agonism is FDA APPROVED for Obesity…
- Considerable evidence now supports aggressive interventions in patients with prediabetes or soon after the diagnosis of type 2 diabetes, to limit the many complications of the disease.
Technology

- Needles (32 guage), U-500 syringe,
- Sensors (Medtronic, DEXCOM, Abbott
- Pumps (Medtroninc, Animas, Tandem)
- Modification of “natural” hormones to increase duration of action and compliance. (Insulins and GLP-1’s mixed injectable Rx, Xultophy, Lixilan)
- Combined Therapies
- Insulins (U-100, U-200, U-300, U-500)
- Bariatric Surgery, (sleeve, Roux en Y)
- Islet (Pancreatic) transplantation
Degludec, a truly “basal” insulin, less variability

* Not yet approved
Integration of pumps with Continuous Glucose Monitor
Artificial Pancreas...Closed Loop)

With a CGMS will “suspend” insulin.
Endocrinology Drug and Device

- Metforin use to GFR of 30
- MiniMed 670G; Hybrid closed loop insulin delivery system
- Expanded indication for the SGLT-2 inhibitor (reduces risk of CV death (secondary prevention) the relative reduction of 32% in the risk of death from any cause
- Dexcom G5(replaces fingerstick blood glucose testing)
Summary: Treatment.

- Although this paradigm shift, which is based upon pathophysiology, represents a “novel” approach to the treatment of type 2 diabetes, it is substantiated by a vast body of basic scientific and clinical investigational studies.
- Because this algorithm is based upon the reversal of known pathophysiological defects, it has a high probability of achieving durable glycemic control.
- If the plasma glucose concentration can be maintained within the normal nondiabetic range, the microvascular complications of the disease, which are costly to treat and associated with major morbidity and mortality, can be prevented.
- Considerable evidence now supports aggressive interventions in patients with prediabetes or soon after the diagnosis of type 2 diabetes to limit the many complications of the disease.
- Most importantly, this will enhance the quality of life for all diabetic patients.
Final thoughts

- A patient-centered approach should be used to guide choice of pharmacological agents.
- Considerations include efficacy, cost, potential side effects, pathophysiology, effects on weight gain, comorbidities, hypoglycemia risk, and patient preferences.
Quotes:

- “You have to find out where you are before you can get to where you're going,” — Richard Jackson, MD
- One should never consider measures to prevent diabetes be inherently different from those used to treat the illness,” — Zachary T. Bloomgarden, MD
- “Rethink diabetes care with an open mind,” Misha Denham, DO
Before and After

One of the first patients to ever receive insulin therapy
References


