Type 2 Diabetes Mellitus
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Disclosure
Michael McDermott MD

No Conflict of Interest to Disclose
Talk Objectives

1. Explain the pathophysiology that underlies current therapies for type 1 and type 2 diabetes mellitus.

2. Emphasize the importance of individualization of A1C targets and drug choices.

3. Discuss practical aspects of initiating and adjusting old and new therapeutic agents for diabetes mellitus.
Diabetes Mellitus

Diagnosis 2014

Diabetes Mellitus
Fasting Glucose $> 125 \text{ mg/dl}$
2 Hour PP Glucose $> 200 \text{ mg/dl}$
A1C $> 6.5\%$

Pre-Diabetes
Fasting Glucose: 100-125 mg/dl
2 Hour PP Glucose: 140-200 mg/dl
A1C: 5.7-6.4\%

Consensus Recommendation: ADA, EASD, IDF 2009
Diabetes Mellitus
28 Million Americans

- Type 2 DM: 95%
- Type 1 DM: 5%

Leading US Cause
- Myocardial Infarction
- Kidney Failure
- Amputations
- Blindness

1 New Case Every 17 Seconds
5,000 New Cases Every Day
2,000,000 New Cases Every Year
Pre-Diabetes
79 Million Americans

Progression to Type 2 Diabetes
11% per Year

Prevention of Progression
Lifestyle Measures: ↓ 60%
Metformin: ↓ 30%

Pan XR, Diabetes Care 1997; 20:537-44. Da Qing Study
United States
Density of One Fast Food Chain

The Contiguous United States
Visualized by distance to the nearest McDonald's

Created by Stephen Von Worley
http://www.weatherseal.com/hugs/mappn/
Location data courtesy of AggData
http://www.aggdata.com/
Exercise
Exercise
The Evolution of Man
Type 2 Diabetes Mellitus

Pathophysiology

↑ Glucose Production

↓ CNS Effect

↓ Insulin Secretion

↑ Insulin Resistance

↓ Incretin Effect

Hyperglycemia
Diet

Ideal Diet for DM: No Consensus

Mediterranean May Be Best

Main Goal
Calorie Restriction

1 lb = 3500 kcal

Deficit: 500 kcal/day
Loss of 1 lb/week
Loss of 52 lb/year

“Well, the Parkers are dead. ... You had to encourage them to take thirds, didn’t you?”
Exercise

Walk 30 Minutes Daily

- 130 kcal/day

Loss of 1 lb in 27 days
Loss of 14 lb in 1 year

The 100 Meter Mosey
Weight Loss

3500 kcal = 1 lb
Type 2 Diabetes Mellitus
Medication Development

1920               1960                        1990                  2000                  2010

- Insulin
- Sulfonylureas
- Metformin

- Rapid Acting Insulins
- Basal Insulins
- Thiazolidinediones
- Meglitinides
- GLP-1 Analogs
- DPP4 Inhibitors
- Colesevelam
- Bromocriptine
- SGLT2 Inhibitors
- Pramlintide
- Colesevelam
- Bromocriptine
Type 2 Diabetes Mellitus
Pathophysiology Based Therapy

- ↓ Glucose Production
- ↓ Insulin Resistance
- ↑ Glycosuria
- ↑ SGLT-2 Inhibitor
- ↑ GLP-1 Analog
- ↑ DPP4 Inhibitor
- ↑ CNS Effect
- ↑ Insulin Secretion
- ↑ Incretin Effect

Euglycemia

- Bromocriptine
- Metformin
- Thiazolidinedione
- Sulfonylurea
- Meglitinide
- Bile Acid Resin
- Glucosidase Inhibitor

↓ Glucose Absorption
↓ Glicose Uriea
Incretin Physiology

- **GLP-1 (Glucagon Like Peptide-1)**
  - **T1/2 = 2 min** due to DPP4
  - **GLP-1** = Glucagon Like Peptide-1
  - **DPP4** = Dipeptidyl Peptidase 4

- **L-Cells**
  - **GLP-1** production

- **Insulin**
  - ↑ Insulin
  - ↓ Glucagon

- **Glucose**
  - ↓ Glucose Production

- **Appetite**
  - ↓ Appetite
  - ↑ Satiety

- **Gastric Emptying**
  - ↓ Gastric Emptying

- **Glucose Dependent**
GLP-1 Analog / Agonist

- Resistant to DPP4 Action
- Prolonged Duration of Analog Action

DPP4 Inhibitor

- Prevents Native GLP-1 Breakdown
- Prolongs Duration of Native GLP-1 Action
Incretin Based Therapy

GLP-1 Analog: DPP4 Resistant
- Exenatide (Byetta)
- Liraglutide (Victoza)
- Exenatide QW (Bydureon)

DPP4 Inhibitor: Inhibit GLP-1 Breakdown
- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)
- Alogliptin (Nesina)
Sodium Glucose Transporter 2 Inhibitors

Kidneys Filter + Reabsorb
Glucose: 180 g/day
90% through SGLT2

Normal

Glycosuria
BG > 180 mg/dl

SGLT2 Inhibitor

Glycosuria
BG > 80 mg/dl

Glucose Loss
80-100 g/day
320-400 kcal/day
## Sodium Glucose Transporter 2 Inhibitors

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade Name</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>Invokana</td>
<td>100, 300 mg</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Luseogliflozin</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Ipragliflozin</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Tofogliflozin</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>ISIS 388626</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>EGT 1747</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>LX 4211</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>
Colestevelam

Mechanism: Impairs Glucose Absorption

Target: Postprandial Glucose

Efficacy: ↓ A1C ~ 0.5%

Name Brand: Welchol (625 mg tabs)

Dose: 3 Tabs BID or 6 Tabs QAM

Additional Benefit: LDL Reduction ~20%

Cost per Month: $225
**Bromocriptine**

**Mechanism:** Reduces Insulin Resistance by Enhancing CNS Dopaminergic Tone

**Target:** Postprandial Glucose

**Efficacy:**
- **Monotherapy** ↓ A1C 0.4-0.6%
- **Add-on Therapy** ↓ A1C 0.6-0.9%

**Name Brand:** Cycloset (0.8 mg tabs)

**Start:** 1 Tab QAM

**Titrate:** ↑ Weekly by 1 Tab to total dose of 2-6 Tabs (1.6 – 4.8 mg) QAM

**Cost per Month:** $299
Personalized Diabetes Care

Individualize

- **A1C Goal**
- **Medications**

Inzucchi S, Diabetes Care 2012; 35:1364-79
Riddle M, Diabetes Care 2012;35:2100-7
Personalized A1C Goal

A1C Goal < 7%

Recent Onset
No / Minimal Hypoglycemia

A1C Goal < 7.5% or < 8%

Known Cardiovascular Disease
Frequent Hypoglycemia
Short Life Expectancy
Advanced Age

Inzucchi S, Diabetes Care 2012; 35:1364-79
Riddle M, Diabetes Care 2012;35:2100-7
Personalized Diabetes Care

Individualize

A1C Goal

Medications
## Type 2 Diabetes: Personalized Medication Choices

<table>
<thead>
<tr>
<th>BG Target</th>
<th>Effect</th>
<th>Low BG</th>
<th>Weight</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FBG &gt; PPBG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>++</td>
<td>No</td>
<td>---</td>
<td>+</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>++</td>
<td>No</td>
<td>↑</td>
<td>++</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>+++</td>
<td>Yes</td>
<td>↑</td>
<td>++</td>
</tr>
<tr>
<td><strong>PPBG &gt; FBG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>++</td>
<td>Yes</td>
<td>↑</td>
<td>+</td>
</tr>
<tr>
<td>DPP4 Inhibitor</td>
<td>+</td>
<td>No</td>
<td>---</td>
<td>+++</td>
</tr>
<tr>
<td>GLP-1 Analog</td>
<td>++</td>
<td>No</td>
<td>↓</td>
<td>+++</td>
</tr>
<tr>
<td>SGLT-2 Inhibitor</td>
<td>+</td>
<td>No</td>
<td>↓</td>
<td>+++</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>+</td>
<td>Yes</td>
<td>↑</td>
<td>++</td>
</tr>
<tr>
<td>Glucosidase Inhibitor</td>
<td>+</td>
<td>No</td>
<td>---</td>
<td>++</td>
</tr>
<tr>
<td>Bile Acid Resin</td>
<td>+</td>
<td>No</td>
<td>---</td>
<td>+++</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>+</td>
<td>No</td>
<td>---</td>
<td>+++</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>+</td>
<td>No</td>
<td>↓</td>
<td>+++</td>
</tr>
<tr>
<td>Prandial Insulin</td>
<td>+++</td>
<td>Yes</td>
<td>↑</td>
<td>++</td>
</tr>
</tbody>
</table>
Type 2 Diabetes Mellitus: Personalized Management

Lifestyle Intervention + Metformin

3 MOS A1C > Goal → Add:

GLP-1 Analog
- Wt Loss
- No Hypo

DPP4 Inhibitor
- Wt Neutral
- No Hypo

SGLT-2 Inhibitor
- Wt Loss
- No Hypo

Basal Insulin
- Most Effective

TZD
- No Hypo

SU
- Low Cost

Bile Acid Resin
- LDL Reduction

Glucosidase Inhibitor
- No Hypo

Bromocriptine
- No Hypo

Pramlintide
- Wt Loss
- No Hypo

Basal/Bolus Insulin
- Most Effective

MTM adapted from Inzucchi S, Diabetes Care 2012; 35:1364-79
Emergency Hospitalizations for Adverse Drug Events
Older U.S. Adults, 2007–2009

Commonly Implicated Agents
- Warfarin
- Insulins
- Oral antiplatelet agents
- Oral hypoglycemic agents
- Opioid analgesics
- Digoxin

High-Risk or Potentially Inappropriate Medications
- HEDIS
- Beers criteria
- Beers criteria excluding digoxin

No. of Hospitalizations per 10,000 Outpatient Medication Visits
Hypoglycemia

Veterans
Hypoglycemia in DM2
2 x ↑ Risk CV Events
Zhao Y

ACCORD
Hypoglycemia in DM2
↑ Mortality Rate
Seaquist E

DM1 and DM2
Hypoglycemia
3.4 x ↑ Risk Mortality
McCoy R

Zhao Y, Diabetes Care 2012; 35:1126-32
Seaquist E, Diabetes Care 2012; 35:409-14
McCoy R, Diabetes Care 2012; 35:1897-1901
## DM2 Medications: Hypoglycemia

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Rare Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Metformin*/**</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>DPP4 Inhibitor**</td>
</tr>
<tr>
<td>Sulfonylurea*</td>
<td>Bromocriptine**</td>
</tr>
<tr>
<td></td>
<td>Bile Acid Resin**</td>
</tr>
<tr>
<td></td>
<td>Glucosidase Inhibitor**</td>
</tr>
<tr>
<td></td>
<td>GLP-1 Analog***</td>
</tr>
<tr>
<td></td>
<td>SGLT-2 Inhibitor***</td>
</tr>
<tr>
<td></td>
<td>Pramlintide***</td>
</tr>
<tr>
<td></td>
<td>Thiazolidinedione</td>
</tr>
</tbody>
</table>

* Inexpensive
** Weight Neutral
*** Weight Loss
# DM2 Medications: Weight Change

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Weight Neutral</th>
<th>Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinedione</td>
<td>Metformin*</td>
<td>GLP-1 Analog</td>
</tr>
<tr>
<td>Insulin**</td>
<td>DPP4 Inhibitor</td>
<td>SGLT-2 Inhibitor</td>
</tr>
<tr>
<td>Meglitinide**</td>
<td>Bile Acid Resin</td>
<td>Pramlintide</td>
</tr>
<tr>
<td>Sulfonylurea*/**</td>
<td>Bromocriptine</td>
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</tr>
</tbody>
</table>

* Inexpensive

** Hypoglycemia
<table>
<thead>
<tr>
<th>eGFR</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td><strong>Full Dose Metformin Appropriate</strong></td>
</tr>
<tr>
<td></td>
<td>Monitor Renal Function Annually</td>
</tr>
<tr>
<td>45-59</td>
<td><strong>Full Dose Metformin Appropriate</strong></td>
</tr>
<tr>
<td></td>
<td>Monitor Renal Function Q 3-6 Months</td>
</tr>
<tr>
<td>30-44</td>
<td><strong>Half Dose Metformin With Caution</strong></td>
</tr>
<tr>
<td></td>
<td>Monitor Renal Function Q 3 Months</td>
</tr>
<tr>
<td>&lt; 30</td>
<td><strong>Stop / Avoid Metformin</strong></td>
</tr>
</tbody>
</table>

Lipska KJ. Diabetes Care 2011; 34: 1431-7
Ekstrom N, BMJ 2012; ePub ahead
Inzucchi S, Diabetes Care 2012; 35: 1364-79
Insulin
The Big Gun
## Insulin Preparations

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro</td>
<td>5-15 min</td>
<td>1-2 hr</td>
<td>3-5 hr</td>
</tr>
<tr>
<td>Aspart</td>
<td>10-20 min</td>
<td>1-3 hr</td>
<td>3-5 hr</td>
</tr>
<tr>
<td>Glulisine</td>
<td>5-20 min</td>
<td>1-3 hr</td>
<td>3-5 hr</td>
</tr>
<tr>
<td>Glargine</td>
<td>1-4 hr</td>
<td>none</td>
<td>22-24 hr</td>
</tr>
<tr>
<td>Detemir</td>
<td>1-4 hr</td>
<td>none</td>
<td>20-24 hr</td>
</tr>
<tr>
<td>Regular</td>
<td>30-60 min</td>
<td>2-4 hr</td>
<td>6-8 hr</td>
</tr>
<tr>
<td>NPH</td>
<td>1-4 hr</td>
<td>8-12 hr</td>
<td>12-20 hr</td>
</tr>
<tr>
<td>Mixes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Insulin Pharmacokinetics

- Lispro / Aspart / Glulisine
- Glargine / Detemir
- Regular
- NPH

Insulin Injection

- 1-2 hr
- 2-4 hr
- 8-12 hr
- +/- 24 hr
- +/- Peakless

4-5 hr 6-8 hr 12-16 hr 24 hr
Basal Insulin Therapy

Indications

- A1C > 11%
- FBG > 250 mg/dl
- Random BG > 300 mg/dl
- Ketonuria / Ketonemia
- Weight Loss, Polydipsia, Polyuria
- A1C > Goal on 1-3 Oral Agents
# Basal Insulin Therapy

**Initiate and Titrate**

Glargine / Detemir / NPH HS

**Start:** 10-25 U Daily  
**Check:** FBG x 2-3 Days

Based on AM FBG, Adjust (choose):

<table>
<thead>
<tr>
<th>Mean AM FBG</th>
<th>Adjust 1 U</th>
<th>Adjust 2 U</th>
<th>Adjust 3 U</th>
<th>Adjust 4 U</th>
<th>Adjust 5 U</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 130</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>80-130</td>
<td>No Δ</td>
<td>No Δ</td>
<td>No Δ</td>
<td>No Δ</td>
<td>No Δ</td>
</tr>
</tbody>
</table>

**Average Basal Dose (DM2)**

0.4-0.5 U/kg or 0.25 U/lb
Basal Insulin Therapy

Adjusting Basal to Control AM FBG

Goal:
AM FBG 80-130

Summary
Start: 10-25 U Daily
Titrate: ↑ by 1-5 U every 2-3 days until AM FBG 80-130
Mealtime Insulin Therapy

Indications

- **A1C > Goal** – AM FBG at Goal

- **PPBG > Goal** – AM FBG at Goal
Basal Plus Insulin
Initiate and Titrate

Lispro / Aspart / Glulisine

**Start:** 4-10 U at **Largest Meal** (Dinner Usually)

**Titrate:** Check BG at **Bedtime or Before Next Meal**

Depending on Meal Covered, Adjust Until:

- HS BG < 140 mg/dl, OR
- BG before Next Meal < 130 mg/dl

Next (if needed): Add Bolus at 2\textsuperscript{nd} Largest Meal

Next (if needed): Add Bolus at 3\textsuperscript{rd} Meal
Basal Plus Insulin

Adjusting Bolus Insulin at Dinner

Goal: HS BG < 140

Alternative Goal: 2 Hr PPBG < 180 mg/dl
Goal:
Pre-Dinner BG < 130

Alternative Goal: 2 Hr PPBG < 180 mg/dl
**Basal Bolus Insulin**

Initiate and Titrate

Lispro / Aspart / Glulisine

**Start:** 4-5 U at Each Meal

**Titrate:** Check Pre-Meal BG and HS BG Daily

**Adjust Until:**

BG before Each Meal < 130 mg/dl, AND

HS BG < 140 mg/dl

**Consider:** Carbohydrate Counting / Flexible Dosing

Using C:I Ratio and Correction Factor (CF)
Basal Bolus Insulin

Adjusting Bolus with Each Meal

Goal:
Next Pre-Meal BG < 130

Goal:
HS BG < 140

Alternative Goal: 2 Hr PPBG < 180 mg/dl

Goal:
AM FBG 80-130

Average Total Daily Dose (DM2)
0.8-1.0 U/kg or 0.4 U/lb
Obesity Treatment as DM2 Strategy

Medications – FDA Approved

Phentermine: $\downarrow$ appetite
Phentermine / Topiramate (Qsymia): $\downarrow$ appetite
Lorcaserin (Belviq): $\downarrow$ appetite
Orlistat (Xenical, Alli): $\downarrow$ fat absorption
GLP-1 Analogs: $\downarrow$ appetite [DM2]
SGLT2 Inhibitors: $\uparrow$ urine glucose [DM2]

Indications:
BMI > 30 kg/m²
BMI > 25 kg/m² with obesity related disease
Phentermine / Topiramate (Qsymia)

Weight Effects

Wt Loss 10-12%

Gadde K, Lancet 2011; 16;377(9774):1341-52
## Phentermine / Topiramate (Qsymia)

### Glucose Effects

743 Patients (BMI 27-45):
Prediabetes (292), Metabolic Syndrome (451)

**RCT:** Q 7.5/46 mg, Q15/92 mg, or Placebo (Lifestyle) x 108 weeks

<table>
<thead>
<tr>
<th></th>
<th>Qsymia 7.5/46 mg</th>
<th>Qsymia 15/92 mg</th>
<th>Lifestyle + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight Loss</strong></td>
<td>10.9%</td>
<td>12.1%</td>
<td>2.5%</td>
</tr>
<tr>
<td><strong>DM2 Prevention</strong></td>
<td>70.5%</td>
<td>78.7%</td>
<td></td>
</tr>
</tbody>
</table>
Phentermine / Topiramate (Qsymia)

Clinical Notes

- **Combination:** greater efficacy, fewer side effects
- **Weight Loss:** 10-12% (20-24 lb for 200 lb person)
- **Doses (Phentermine / Topiramate):**
  
  3.75/23 mg, 7.5/46 mg, 15/92 mg

- **Cost:** $150.00/month
- **Off-Label:** use of generic Phentermine + Topiramate
Lorcaserin (Belviq)
Weight Effects

Wt Loss
4-5%

Lorcaserin (Belviq)
Glucose Effects

604 DM2 Patients (BMI 27-45):
RCT: Lorcaserin 10 mg QD vs 10 mg BID vs Placebo x 1 Year

O'Neil PM, Obesity 2012; 20:1426-36
Lorcaserin (Belviq)
Clinical Notes

- Serotonin 2C Receptor Agonist → Satiety
- Weight Loss: 4-5% (8-10 lb for 200 lb person)
- Previous Serotonin Agonists: Dexfenfluramine + Fenfluramine caused cardiac valve disease
- 2C Receptor: in Brain only and not in Heart
- Lorcaserin: No Evidence of Heart Valve Disease
- Cost: $?/month
- Off-Label: Use with Phentermine (unclear safety)
Treatment of Obesity

Bariatric Surgery

Multiple Surgery Types Available

**Indications:**
- BMI > 40 kg/m²
- BMI > 35 kg/m² with obesity related disease
Bariatric Surgery
Weight Loss – 15 Years

Control
Banding  14%
Vertical Banded Gastroplasty  16%
Gastric Bypass  25%

Study of Obese Subjects (SOS)
Bariatric Surgery
Mortality – 15 Years

Study of Obese Subjects (SOS)
Randomized Trial: 43 Obese DM2 Patients
Roux-en-Y Surgery vs Intensive Lifestyle and Medications
One Year Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Roux-en-Y Surgery</th>
<th>Lifestyle + Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss</td>
<td>25.8%</td>
<td>6.4%</td>
</tr>
<tr>
<td>DM2 Remission</td>
<td>60%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Bariatric Surgery

Mortality Rate: < 1%
Adverse Events: ~ 20%

Beneficial Effects:
- Cardiovascular Disease
- Diabetes Mellitus
- Hyperlipidemia
- Hypertension
- Sleep Apnea
- Mortality

Buchwald, JAMA 2004; 292:1724
Maggard, Ann Intern Med 2005; 142:547
DeMaria E, NEJM 2007; 356:2176
Sjostrom L, NEJM 2007; 357:741
EndoBarrier
Summary of Type 2 Diabetes Management

- Obesity is the most important risk factor for DM2
- Lifestyle modification can prevent DM2 and must be part of all DM2 management plans
- DM2 results from excess hepatic glucose production, insulin resistance and relative insulin deficiency
- Medications are available to address the multiple known pathophysiological factors in DM2
- A1C ≤ 7% prevents microvascular complications
- Hypoglycemia should be avoided
- Glycemic goals and therapy should be personalized
- Obesity treatment beneficial for DM2 management
Thank You
Appendix
Type 2 Diabetes Mellitus
Prevention and Treatment
Lifestyle Modification

Diet
- No consensus regarding ideal diet for DM
- Main Goal: Calorie Restriction
  - 1 lb = 3500 kcal
  - 500 kcal/d deficit = 1 lb/week = 52 lb/year

Exercise
- Walk 30 min/day ~ 130 kcal
  - 130 kcal/d deficit = 1 lb/27 days = 14 lb/yr

Weight Loss
Metformin

Mechanism:
- Reduce insulin resistance (liver > muscle)
- Reduce hepatic glucose production

Products available
- Metformin
- Glucophage XR
- Glumetza

Start: 500 mg qd short acting preparation;
\[ \uparrow \] weekly to 2000-2500 mg qd (BID dosing)

Start: 1000 mg qd long acting preparation;
\[ \uparrow \] to 2000 mg qd in 1-2 weeks (QD dosing)

Avoid: eGFR \( \leq 30 \) ml/min; Severe liver disease
Thiazolidinediones

Mechanism:
- Reduce insulin resistance (fat, muscle, liver)

Products available
- Pioglitazone (Actos)
- Rosiglitazone (Avandia)

Start: low or middle dose; ↑ every 4-6 weeks, as needed, to highest dose

Avoid: Class 2-4 CHF; significant edema; Liver disease (except NASH)

Caution: Chronic renal failure (edema) Bladder cancer
Sulfonylureas

Mechanism: stimulate insulin secretion

Products available

- Glyburide
- Glipizide, Glipizide XL/ER
- Glimepiride (Amaryl)

Start: low, ↑ to maximum dose, as needed

Avoid: Chronic renal failure (Glipizide OK)
Meglitinides

**Mechanism:** stimulate insulin secretion

**Products available**
- Repaglinide (Prandin)
- Nateglinide (Starlix)

**Start:** lowest dose before each meal;

↑ to highest dose TID, as needed

**Avoid:** Chronic renal failure (Repaglinide OK)
Incretin Based Therapy

Mechanism: Glucose-dependent **Insulin Stimulation**

Glucose-dependent **Glucagon Suppression**

**GLP-1 Analog / Agonist**

Exenatide (Byetta): Start 5 mcg BID; ↑ to 10 mcg BID in 1 month

Liraglutide (Victoza): Start 0.6 mg QD, ↑ to 1.2 mg QD in 2 wks,

↑ to 1.8 mg QD in 2 wks

Exenatide QW (Bydureon): 2 mg QW

**DPP4 Inhibitor**

Sitagliptin (Januvia): 100 mg QD (↓ dose in renal failure)

Saxagliptin (Onglyza): 2.5 or 5 mg QD (↓ dose in renal failure)

Linagliptin (Tradjenta): 5 mg QD (no dose change in renal failure)

Alogliptin (Nesina): 25 mg (↓ dose in renal failure)
Amylin Based Therapy

Mechanism: Glucagon Suppression
Postprandial Glucose Reduction

Products available

- Pramlintide (Symlin)

Type 1 DM:
Start 15 ug TID. ↑ q 3 days to 30 ug TID, to 45 ug TID, and to 60 ug TID.

Type 2 DM:
Start 60 ug TID. ↑ in 3-7 days to 120 ug TID.
Flexible Mealtime Bolus Insulin

**Bolus Components**

**C:I Ratio:** Gm of Carb covered by 1U Insulin  
**CF:** Expected BG drop from 1U Insulin  
Add if pre-meal BG high

**Starting Calculations at UCH**

C:I = 500/TDD (~15:1)  
CF = 1650/TDD (~50:1)

**Goal for Dose Adjustment**

2 Hr PPBG < 180 mg/dl  
Next Pre-meal BG < 130 mg/dl  
PPBG 30-50 mg/dl above Pre-meal BG