Advances in Type 2 Diabetes Care

Neelima Chu, MD, FACE
Sharp Rees-Stealy
Department of Endocrinology
Objectives

» Review the pathophysiology of Type 2 Diabetes
» Understand the goals of diabetes care
» Review the older diabetes medications
» Learn the mechanism of action of the newer diabetes medications (including injectables)
» Assess the use and safety during inpatient admission
Pathogenesis of Type 2 Diabetes

◆ The environmental risk factors: increased weight gain and decreased physical activity

◆ Three key fundamental defects to the development and progression of T2DM:
  ◆ impaired insulin secretion from pancreatic β-cells
  ◆ decreased glucose uptake in peripheral tissues
  ◆ increased hepatic glucose production (HGP)

◆ Treatment is based on targeting these defects
Natural History of Type 2 Diabetes

Glucose (mg/dL)

- 350
- 300
- 250
- 200
- 150
- 100
- 50

Relative Function (%)

- 250
- 200
- 150
- 100
- 50
- 0

Years of Diabetes

- 10
- 5
- 0
- 5
- 10
- 15
- 20
- 25
- 30

Obesity

IFG* 

Diabetes

Uncontrolled hyperglycemia

Postmeal glucose

Fasting glucose

Insulin resistance

Insulin level

β-cell failure

*IFG = impaired fasting glucose.

Adapted from International Diabetes Center (Minneapolis, Minn).
American Diabetes Associations Recommendations

- Glycosylated hemoglobin: <7.0%
- Pre-prandial plasma glucose: 90-130mg/dl
- Postprandial plasma glucose: <180mg/dl
The overall HbA1c achieved was 0.9% lower in the intensive compared with the conventional (7.0% vs. 7.9%).

The difference in glycemic control was associated with a reduction in the risk of microvascular complications (retinopathy, nephropathy, neuropathy).

A trend toward reduced rates of myocardial infarction.
Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

- Patient-centered care is defined as an approach to “providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patients values guide all clinical decisions”
Approach to management of hyperglycemia:

- **More stringent**
  - Patient attitude and expected treatment efforts: Highly motivated, adherent, excellent self-care capacities
  - Risks potentially associated with hypoglycemia, other adverse events: Low
  - Disease duration: Newly diagnosed
  - Life expectancy: Long
  - Important comorbidities: Absent
  - Established vascular complications: Absent
  - Resources, support system: Readily available

- **Less stringent**
  - Patient attitude and expected treatment efforts: Less motivated, non-adherent, poor self-care capacities
  - Risks potentially associated with hypoglycemia, other adverse events: High
  - Disease duration: Long-standing
  - Life expectancy: Short
  - Important comorbidities: Few / mild
  - Established vascular complications: Few / mild
  - Resources, support system: Limited
Healthy eating, weight control, increased physical activity, and diabetes education

Metformin

- High efficacy, low risk, neutral/lack of GI/lactic acidosis, low cost.

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

- Metformin + Sulfonylurea: high efficacy, moderate risk, low risk of hypoglycemia, low cost.
- Metformin + Thiazolidinedione: high efficacy, high risk, gain in edema, HF, or fluid.
- Metformin + DPP-4 inhibitor: intermediate efficacy, low risk, rare, high.
- Metformin + SGLT2 inhibitor: intermediate efficacy, high risk, loss in GU, dehydration, high.
- Metformin + GLP-1 receptor agonist: high efficacy, highest risk, gain in hypoglycemia, variable.
- Metformin + Insulin (basal): highest efficacy, highest risk, gain in hypoglycemia, variable.

If HbA1c target not achieved after ~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- and disease-specific factors):

- Metformin + Sulfonylurea + TZD: high efficacy, moderate risk, low risk of hypoglycemia, low cost.
- Metformin + Thiazolidinedione + SU: high efficacy, high risk, gain in edema, HF, or fluid.
- Metformin + DPP-4 inhibitor + TZD: intermediate efficacy, low risk, rare, high.
- Metformin + SGLT2 inhibitor + SU: intermediate efficacy, high risk, loss in GU, dehydration, high.
- Metformin + GLP-1 receptor agonist + SU: high efficacy, highest risk, gain in hypoglycemia, variable.
- Metformin + Insulin (basal) + TZD: highest efficacy, highest risk, gain in hypoglycemia, variable.

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i.

- Metformin + Basal insulin + Mealtimes insulin or GLP-1-RA.
GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGi
- SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

If not at goal in 3 months proceed to Triple Therapy

Entry A1C > 9.0%

SYMPTOMS
NO
- DUAL Therapy
YES
- INSULIN
  ± Other Agents
  OR
  TRIPLE Therapy

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND
- Few adverse events and/or possible benefits
- Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE
Sulfonylureas
Meglitinides

◆ Most widely used drugs

◆ The SFU (glyburide, glipizide, glimepride) and meglitinides (Prandin, Starlix) are structurally different but act similarly by increasing insulin secretion
Metformin

- Decreases gluconeogenesis
- Increases insulin-mediated glucose utilization in peripheral tissues (such as muscle and liver)
Thiazolidinediones (TZD) (Actos, Avandia)

- TZDs bind to and activate peroxisome proliferator-activated receptors (PPARs)

- TZDs increase insulin sensitivity by acting on adipose, muscle, and liver to increase glucose utilization and decrease glucose production
α- Glucosidase Inhibitors
(Acarbose, Miglitol)

- These drugs slow absorption of glucose
- The main side effects are flatulence and diarrhea
Bromocriptine (Cycloset)

- The mechanism of action in reducing blood sugar is unknown
- Not generally recommended for the treatment of type 2 diabetes
Colestevlam (Welchol)

- A bile acid sequestrant
- Mechanism of action to improve glycemic control is uncertain
- Generally not recommended to improve glycemic control
The incretin hormones GLP-1 and GIP are secreted from the intestine in response to meals.

- Slows gastric emptying
- Inhibits post-meal glucagon release and reduces food intake
- GLP-1 exhibits a short half-life of one to two minutes due to degradation by the enzyme dipeptidyl peptidase 4 (DPP-4)
GLP-1 Analogs

Daily
- Exenatide (Byetta)
- Liraglutide (Victoza)

Weekly
- Exenatide (Bydureon)
- Albiglutide (Tanzeum)
- Dulaglutide (Trulicity)
DPP-4 Inhibitors

- They increase the GLP-1 levels
- Stimulates the release of insulin
- Decreases the levels of glucagon in the circulation
- Can be administered orally
- No risk of hypoglycemia
DPP-4 Inhibitors

- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)
- Alogliptin (Nesina)
SGLT-2 (Sodium-Glucose Co-Transporter-2)

Limited Reabsorption

90% Reabsorption

Limited Reabsorption
Glucose excretion

SGLT-2 Inhibitor

Lower Blood Glucose Levels
SGLT-2 Inhibitors

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
SGLT-2 Inhibitors: Caution and Side Effects

- SGLT2 inhibitors **should not** be used in:
  - Type 1 diabetes
  - Type 2 diabetes and eGFR <60 mL/min (dapagliflozin) or <45 mL/min (canagliflozin, empagliflozin)
  - Ketosis-prone type 2 diabetes
- The most common side effects: vulvovaginal candidal infections and hypotension, acute kidney injury, urinary tract infections, euglycemic diabetic ketoacidosis
Traditional Insulins And Their Time Course Of Action

Premixed insulin also Available (70/30, 75/25)

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting</strong></td>
<td>10-15 mins</td>
<td>60-90 mins</td>
<td>4-5 hr</td>
</tr>
<tr>
<td><strong>Regular</strong></td>
<td>30-60 mins</td>
<td>2-4 hours</td>
<td>5-8 hr</td>
</tr>
<tr>
<td><strong>NPH</strong></td>
<td>1-3 hr</td>
<td>5-8 hours</td>
<td>12-18 hr</td>
</tr>
<tr>
<td><strong>Detemir</strong></td>
<td>90 mins</td>
<td>Relatively Peakless</td>
<td>12-24 hr</td>
</tr>
<tr>
<td><strong>Glargine</strong></td>
<td>90 mins</td>
<td>Peakless</td>
<td>24 hr</td>
</tr>
</tbody>
</table>

Newer Insulins

- Afreeza
- U 300 Glargine: Tresiba
- Degludec U 100, U200: Tresiba
- U 500 Humulin Pen
Afrezza: Rapid Acting Inhaled Insulin

- Administered at the start of a meal
- Dissolves immediately upon inhalation
- Peak insulin levels are achieved within 12 to 15 minutes of administration
Dosing Units For Inhaled Insulin

<table>
<thead>
<tr>
<th>Injected Mealtime Insulin Dose</th>
<th>AFREZZA® Dose</th>
<th># of 4 unit (blue) cartridges needed</th>
<th># of 8 unit (green) cartridges needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 4 units</td>
<td>4 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-8 units</td>
<td>8 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-12 units</td>
<td>12 units</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>13-16 units</td>
<td>16 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-20 units</td>
<td>20 units</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>21-24 units</td>
<td>24 units</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
U300 Glargine: Toujeo

- 3x concentration of Glargine
- U300 is a new formulation of insulin glargine that is expected to last up to 40h
- Lower risk of hypoglycemia
- Get more insulin with smaller volume
- More stable levels than Lantus
**Toujeo (U-300) vs Lantus (U-100)**

1. Flatter and longer duration of action
2. Less peaks and valleys
3. Less hypoglycemia
Degludec:  
Tresiba U100, U200

- Onset of action is 2 hours
- Duration of effect: 40 hours
- No peak effect
- Less hypoglycemia
Degludec: Tresiba

Relative serum trough concentrations of once-daily dosing in adults with type 1 diabetes\textsuperscript{2,3}

STEADY STATE ACHIEVED AFTER 3 TO 4 DAYS\textsuperscript{1}
Humalog U-200 Kwik Pen

- Concentrated Humalog, short acting insulin
- Comes in a pen only
- 2x concentrated as Humalog 100u/ml
- You take the same dose but inject less volume and the pen will last longer
U 500 Humulin

- Concentrated insulin indicated to improve glycemic control in those requiring more than 200 units of insulin per day
- Comes in a 20 ml Vial or Pen
- 5x concentrated regular insulin
- Usually given 2-3 x day
U100, U200, U300, U500
Are U confused?

- U100 = 100 units of insulin / 1 ml
- U200 = 200 units of insulin / 1 ml
- U300 = 300 units of insulin / 1 ml
- U500 = 500 units of insulin / 1 ml

If you want to give a pt 100 units

U100 = 100 units = 1 cc = 1 ml
U200 = 100 units = 1/2 cc = 0.5 ml
U300 = 100 units = 1/3 cc = 0.3 ml
U500 = 100 units = 1/5 cc = 0.2 ml
Why is Volume Important?

- U100
- U200
- U300
- U500
- U100
Medtronic 530G/Enlite

Dexcom G4 & G5 Platinum

Continuous Glucose Monitoring Devices
# Efficacy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Change in A1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFU</td>
<td>1-2%</td>
</tr>
<tr>
<td>Metformin</td>
<td>1.5%</td>
</tr>
<tr>
<td>Actos</td>
<td>0.5-1.4%</td>
</tr>
<tr>
<td>α Glucosidase Inhibitors</td>
<td>0.5-0.8%</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>0.4-0.5%</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>0.5%</td>
</tr>
<tr>
<td>GLP-1 Analogs</td>
<td>0.9-1.9%</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>0.5-1.5%</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
<td>0.5-0.7%</td>
</tr>
<tr>
<td>Insulins</td>
<td>Unlimited</td>
</tr>
<tr>
<td></td>
<td>MET</td>
</tr>
<tr>
<td>----------</td>
<td>-----</td>
</tr>
<tr>
<td>HYPO</td>
<td>Neutral</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
</tr>
<tr>
<td>RENAL/GU</td>
<td>Contra-indicated CKD Stage 3B,4,5</td>
</tr>
<tr>
<td>GI Sx</td>
<td>Moderate</td>
</tr>
<tr>
<td>CHF</td>
<td>Neutral</td>
</tr>
<tr>
<td>CARDIAC</td>
<td>Benefit</td>
</tr>
<tr>
<td>ASCVD</td>
<td>Benefit</td>
</tr>
</tbody>
</table>

- **Few adverse events or possible benefits**
- **Use with caution**
- **Likelihood of adverse effects**
- **? Uncertain effect**

COPYRIGHT © 2016 AACE MAY NOT BE REPRODUCED IN ANY FORM WITHOUT EXPRESS WRITTEN PERMISSION FROM AACE.
Transition into Hospital

◆ Insulin is the preferred treatment for glycemic control
◆ In certain circumstances, it may be appropriate to continue home regimens
◆ Diabetes self-management in the hospital may be appropriate for select youth and adult patients
◆ Important to keep side effects in mind
Key Points

◆ Glycemic targets and therapies must be individualized
◆ Diet, exercise, and education remain the foundation of any type 2 diabetes treatment
◆ Combination therapy with 1–2 oral or/and injectable agents is reasonable, aiming to minimize side effects where possible
◆ All treatment decisions should be made in conjunction with the patient, focusing on their preferences, needs, and values