Update on Type II Diabetes
Pharmacotherapy

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Disclosures
• I have nothing to disclose

Pharmacist Objectives
• Appreciate the pathophysiology of type II diabetes
• Acknowledge the new treatment options for type II diabetes
• Understand the advantages and disadvantages of novel therapeutic options

Technician Objectives
• Appreciate the effects of type II diabetes in the body
• Identify new medications used in type II diabetes
• Understand how the new medications differ from older diabetes treatment agents
**Diabetes In the U.S.**

- **29.1 million people** have diabetes.
- **86 million people** have prediabetes.
- **$245 billion** in total medical costs and lost work and wages for people with diabetes.

**Type II Diabetes Mellitus (T2DM)**

- Previously referred to as “non-insulin dependent” or “adult-onset”
- Insulin resistance + lack of insulin secretion
- Progressively lower insulin secretion over time
- Increased risk for macrovascular + microvascular complications

**Diabetes**

- **Type I**: 5-10%
- **Type II**: 5-10%
- **Gestational**: 2%
- **Other**: < 5%

**Advances in Diabetes**

- 2013: Commercial production of insulin
- 2015: 1st generation Sulfonylurea (SU)
- 2016: “Insulin-Dependent” vs “Non-Insulin Dependent”
- 2017: GLP-1 becomes preferred method for chronic diabetes glucose management
- 1923: Commercial production of insulin
- 1955: 1st generation Sulfonylurea (SU)
- 1977: A1C becomes preferred method for chronic diabetes glucose management
- 1993: Diabetes Control and Complications Trial (DCCT) published
- 1995: Metformin, acarbose become available. Glucagon-Like Peptide (GLP)-1 discovered
- 2005: Byetta® (exenatide), Januvia® (sitagliptin) approved
- 2008: ACCORD, ADVANCE and VADT are presented at the American Diabetes Association (ADA)
- 2013: Invokana® (canagliflozin) approved
- 2014: Victoza® (liraglutide) approved
Diagnosis

- Two blood tests demonstrating
  - Plasma Glucose Criteria
    - Fasting Plasma Glucose (FPG) ≥ 126 mg/dL
    - 2-h Plasma Glucose ≥ 200 mg/dL
  - A1C Criteria ≥ 6.5%
- Classic symptoms of hyperglycemia + random plasma glucose > 200 mg/dL

Individualization of Glycemic Goals

- American Diabetes Association (ADA)
  - Pre-prandial plasma glucose 80-130 mg/dL
  - Post-prandial plasma glucose < 180 mg/dL
  - A1C < 7%
- American Association of Clinical Endocrinologists (AACE)/ American College of Endocrinology (ACE)
  - Pre-prandial plasma glucose < 110 mg/dL
  - 2-hour post-prandial glucose < 140 mg/dL
  - A1C ≤ 6.5%

Principles of Care

1. Individualization of glycemic goals
2. Lifestyle optimization
3. Pharmacological therapy
   - Patient attributes
   - Minimizing complications
     - Hypoglycemia
     - Weight gain
**Individualization of Glycemic Goals**

- Optimal $A_1C$: 6.5-7%
  - **VS.**

**Lifestyle Optimization: Obesity Management**

- Overweight/obese: 5-15% weight loss
  - Non-pharmacologic: diet, physical activity, behavioral strategies
  - Pharmacological
    - BMI $\geq 27$ kg/m$^2$: weight loss medications
    - Choosing glucose lowering medications that promote weight loss/weight neutral

**Lifestyle Optimization: Obesity Management**

- Delay progression pre-diabetes $\rightarrow$ T2DM
- Improve glycemic control
  - $\downarrow A_1C$: 1-2%, fasting plasma glucose
  - $\downarrow$ need for glucose lowering medications
- Look AHEAD trial
  - Equal risk factor control
  - Fewer glucose, BP, lipid lowering medications

**Pharmacological Therapy**

- **Life style modifications**
- **Initial drug monotherapy: metformin**
- **Two-drug combinations: metformin +**
  - SU
  - T2D
  - DPP-4
  - GLP-1
  - Insulin (basal)
- **Three-drug combinations: metformin +**
  - SU
  - T2D or DPP-4 or GLP-1 or Insulin
- **More complex insulin strategies: multiple daily doses**
Patient Case 1

- RD, a 65 y.o. male, is diagnosed with T2DM

- **PMH:** Obesity (BMI 29.5 kg/m²), HTN, GERD

- **Labs:** \( A_1C \) 8.5%

**What should we recommend for RD?**

a) Lifestyle recommendations including 7% weight loss and physical activity

b) Start metformin 500 mg PO BID with morning, evening meal

c) Start on insulin since it has the highest \( A_1C \) lowering efficacy

d) Metformin 500 mg PO BID + glyburide

**Initial Therapy: Metformin**

- Biguanide, enhances insulin sensitivity
  - \( A_1C \downarrow 1.5\% 
  - Extensive experience

- Side effects
  - Weight loss, mild hypoglycemia
  - GI: diarrhea, nausea, vomiting
  - Boxed Warning: Lactic acidosis

- Low cost

**Anti-Diabetic Medications**

- **SulfonylUrea (SU)**
  - glipizide, glyburide, gliclazide

- **Thiazolidinedione (TZD)**
  - pioglitazone, rosiglitazone

- **Dipeptidyl Peptidase-4 Inhibitor (DPP-4)**
  - sitagliptin, saxagliptin, alogliptin, linagliptin

- **Sodium Glucose co-Transporter-2 (SGLT-2 Inhibitors)**
  - empagliflozin, canagliflozin

- **Glucagon-Like Peptide-1 agonist (GLP-1)**
  - exenatide, liraglutide, albiglutide, dulaglutide

- **Others:** alpha glucosidase inhibitors, pramlintide

* AACE does not rec as a 1st line alternative
Summary of the Anti-Diabetics

<table>
<thead>
<tr>
<th>Criteria</th>
<th>SU</th>
<th>TZD</th>
<th>GLP-1</th>
<th>DPP-4</th>
<th>SGLT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c Lowering</td>
<td>1.5%</td>
<td>1.5%</td>
<td>1%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Weight</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Renal Considerations</td>
<td>GFR &lt; 60 ml/min</td>
<td>None</td>
<td>GFR = 60 ml/min (exenatide)</td>
<td>sitagliptin, saxagliptin, alogliptin</td>
<td>GFR &gt; 60 ml/min</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Nausea, Skin reactions, Heart Failure</td>
<td>Fluid retention, Gl radiation, Heart Failure</td>
<td>Headache, URTI, UTI, Diabetic Ketoacidosis</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Boxed Warnings</td>
<td>None</td>
<td>CHF</td>
<td>Thyroid C-cell tumor risk, None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Patient Case 2

- RD is back 10 weeks later for a follow up
- **Medications**: metformin 1000 mg PO BID
- **Labs**: A1c 8%
- How can we further optimize his therapy?

How can we further optimize his therapy?

a) Add sitagliptin 100 mg PO daily to his regimen
b) Increase metformin dose since he is only on 2000 mg daily
c) Add glyburide 2.5 mg PO daily
d) Do nothing—it has not been long enough to see the full effects of his current regimen
Dual Anti-Diabetic Therapy

- Recommended for
  - $A_1C \geq 7.5\%$ or $9\%$ at baseline
  - Target $A_1C$ not achieved after 3 months
- Adding non-insulin therapy $\downarrow A_1C$ 0.9-1.1%

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GLP-1

SGLT-2 Inhibitors

Insulin Management

Not controlled after FPG at goal?

$A_1C$ 8% ?

Basal Basal-Bolus

≥ 2 rapid insulin injections

Basal: Lantus® (glargine), Levemir® (detemir)

Lentris® (liraglutide), NovoLog® (insulin aspart)

Rapid: Humalog® (lispro), Novolog® (insulin aspart)

AACE vs ADA

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<td>Diagnosis Preference</td>
<td>Plasma Glucose Criteria</td>
<td>$A_1C$ Plasma Glucose Criteria</td>
</tr>
<tr>
<td>BP Goal</td>
<td>$&lt; 130/80 \text{ mmHg}$</td>
<td>$&lt; 140/90 \text{ mmHg}$</td>
</tr>
<tr>
<td>Cholesterol Goal</td>
<td>LDL $&lt; 100 \text{ mg/dL}$, HDL $&gt; 70 \text{ mg/dL}$</td>
<td>Refer to ATP-4</td>
</tr>
</tbody>
</table>

Initiation of Insulin Therapy

- Recommended for
  - $A_1C \geq 10\%$ or plasma glucose $\geq 300 \text{ mg/dL}$
  - Unlikely to reach target $A_1C$
    - 2 anti-diabetic agents + $A_1C > 8\%$
    - Longstanding T2DM

- Start: basal insulin ± metformin ± anti-diabetic

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New Treatment Options

SGLT-2 Inhibitors

- Glucosuric action is independent of insulin
  - ↓ A1c 0.7%
  - Limited efficacy in GFR < 45-60 mL/min
- Side Effects
  - ↓ weight, systolic BP
  - Dehydration, hypotension
  - Slight increases in LDL, HDL
- Post-marketing reports of diabetic ketoacidosis (?)

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<tr>
<th>Criteria</th>
<th>Invokana® (canagliflozin)</th>
<th>Farxiga® (dapagliflozin)</th>
<th>Jardiance® (empagliflozin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Janssen</td>
<td>AstraZeneca</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>Dosing</td>
<td>100-300 mg daily</td>
<td>5-10 mg daily</td>
<td>10-25 mg daily</td>
</tr>
<tr>
<td>GFR Cut-Off</td>
<td>45 mL/min</td>
<td>60 mL/min</td>
<td>45 mL/min</td>
</tr>
<tr>
<td>Class Side Effects</td>
<td>Vulvovaginal candidiasis, UTI, diabetic ketoacidosis (?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td>Hyperkalemia ↑ fractures</td>
<td>Bladder cancer ↑ fractures</td>
<td>↑ All cause + CV death</td>
</tr>
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Afrezza® (Insulin Human)

- Rapid-acting, inhaled before meal
  - Shorter duration vs injectable
  - Supplied as 4, 8, or 12 units
- Boxed warning: Risk of acute bronchospasm has been observed in asthmatics + COPD
New Long Acting Insulins

**Basaglar® (insulin glargine)**
- 1st insulin approved through abbreviated pathway
- Expected cost savings

**Tresiba® (insulin degludec)**
- Ultra long acting basal insulin, “peakless”
  - Duration beyond 42 hours
  - Greater dosing flexibility
- Available as U-100, U-200
- Less hypoglycemia vs insulin glargine

Clinical Trials in Progress..

- Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)
  - Glimepiride
  - Sitagliptin
  - Liraglutide
  - Insulin glargine
  - plus metformin

- Vitamin D and type 2 diabetes (D2d)

- Restoring Insulin Secretion Study (RISE)

In the Pipeline

- Novel combinations
  - Xultophy®: insulin degludec + liraglutide
  - LixiLan®: insulin glargine + lixisenatide

- Novel dosing schedules
  - Marizev®: omarigliptin
  - Semaglutide

- Novel mechanisms
  - Emapticap pegol: diabetic nephropathy
  - Human prolslet Peptide: HiP2B

Conclusion

- T2DM is a multifaceted disease state requiring coordination of care
- Treatment and assessment of goals should be individualized
- Lifestyle optimization and metformin continue to be the cornerstones of therapy
- New and innovative treatment options are underway
References

- Metformin: Drug information. In: Lexicomp®, Online Database. Post, TW (Ed), UpToDate, Waltham, MA. 2016.
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