Disclosures

NONE
Learning Objectives

• Provide the tools on how to use the medications that are now available for diabetes management.

• Discuss the efficacy of the diabetes-related medications.

• Identify cultural and other health belief barriers to insulin use and other therapies for diabetes.
Diabetes Overview
Type 1 Diabetes

- Autoimmune disease that can develop at any age
- Absolute absence of insulin
- Daily insulin administration is required for life
- ~5-10% of all cases of diabetes
- Most prevalent in those of northern European ancestry
Type 2 Diabetes

• Progressive disease related to:
  • A decline in insulin production
  • A loss of first phase insulin release
  • Insulin resistance

• ~90% of all cases of diabetes

• At risk populations include:
  • Hispanic-American, Asian-American, Native American, Pacific Islander, African-American
Gestational Diabetes

- Diabetes diagnosed in third trimester (24-28 weeks) using 75g 2 hour OGTT
- Positive for GDM with any of the following results:
  - Fasting glucose >92mg/dL
  - 1 hour pp >180mg/dL
  - 2 hour pp >153mg/dL
Type 2 Diabetes

Natural History of T2DM and Risk for Complications

- Macrovascular disease risk
- Microvascular disease risk
- Post-meal glucose
- Fasting glucose

Meets ADA diagnostic criteria for T2DM

Time (years)

PG 200 mg/dL

PG 126 mg/dL

Diabetes Diagnosis

Symptoms of diabetes plus random plasma glucose ≥200 mg/dL

or

FPG ≥126 mg/dL

or

2-h plasma glucose during a 75-g OGTT ≥200 mg/dL

or

Hemoglobin A1c >6.5%
Diagnosing Diabetes Type 1 & Latent Autoimmune Diabetes in Adults (LADA): Beyond Glucose

• C-peptide-fasting with BG <250mg/dL
• Glutamic Acid Decarboxylase Autoantibodies (Anti-GAD)
• Insulin Autoantibodies (IAA)
• Insulinoma-Associated-2 Autoantibodies (IA-2A)
• Islet Cell Cytoplasmic Autoantibodies (ICA)-oldest test, not used
• Zinc Transporter 8 (ZnT8Ab)-newest, not widely available yet
IFG and IGT
Intermediate Between Normal and Diabetes

**Impaired Fasting Glucose (IFG)**
- FPG ≥100 but <126 mg/dL
- Predicts increased risk of diabetes and micro- and macrovascular complications

**Impaired Glucose Tolerance (IGT)**
- 2-h PG on OGTT ≥140 but <200 mg/dL
- Predicts increased risk of diabetes and cardiovascular disease
Regulation of Fasting Glucose

- Hepatic glucose production is a primary factor determining fasting plasma glucose.

- Fasting hepatic glucose production is regulated by:
  - Fasting (basal) plasma insulin
  - Hepatic sensitivity to insulin
  - Fasting substrate availability

- In type 2 diabetes:
  - Basal insulin secretion is impaired
  - Hepatic sensitivity to insulin is decreased
Regulation of Postprandial Glucose

- A meal contains 6 to 20 times the glucose content of the blood

- Normally, postprandial hyperglycemia is regulated by
  - Clearance of ingested glucose by the liver
  - Suppression of hepatic glucose production
  - Peripheral clearance of glucose
Goals of Therapy

- **A1c** 7% or lower
- **Blood pressure** 140/90 or lower
- **Cholesterol** 200mg/dL or lower (LDL <100)
- Maintain a healthy body weight
- Prevent/delay complications of unmanaged diabetes
- Maintain quality of life
Non-Insulin Medication Options for Type 2 Diabetes
Medication Therapies in Type 2 Diabetes: Orals

• Sulfonylureas (secretagogues)
  – Glyburide* (Diabeta/Glynase), glipizide* (Glucotrol/Glucotrol XL), glimepiride* (Amaryl), nateglinide*, repaglinide*

• Biguanides
  – Metformin* (Glucophage/Glucophage XR/Glumetza/Fortamet, Riomet)

• Thiazolidinedione aka TZDs
  – Pioglitazone* (Actos), rosiglitazone* (Avandia)

• DPP-4 Inhibitors
  – Sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), alogliptin* (Nesina)

• SGLT2 Inhibitors
  – Dapagliflozin (Farxiga), canagliflozin* (Invokana), empagliflozin* (Jardiance), ertugliflozin (Steglatro)

• Alpha-glucosidase Inhibitors
  – Acarbose* (Precose), miglitol* (Glyset)

• Bile Acid Sequestrants
  – Cholestyramine*, cholestipol*, colesevelam HCL (Wellchol)

• Dopamine agonist
  – Bromocriptine* (Cycloset)
Sulfonylureas

Widely used oral medication in the U.S.

increased cardiovascular risk related to

weight gain

fluid retention

hypoglycemia

No longer recommended as first agent of choice.
Biguanides (metformin)

Benefits of metformin related to improving insulin resistance

- weight management
- fatty liver disease
- cardiovascular disease
  - endothelial function
  - anti-inflammatory agent
  - anti-oxidant

**Biguanides (metformin)**

Benefits in non diabetes related conditions

HIV treatment side effects (insulin resistance)

reduces cancer risk

liver, pancreas, colon, breast, prostate, cervical, renal cell

Risk associated with metformin

vitamin B12 deficiency resulting in worsening neuropathy

should not be used in patients with eGFR <30
SGLT2 Inhibitors

Benefits of therapy beyond glycemic management

Cardiovascular benefits (FDA approval 2018)
- decreased nonfatal heart attack
- decreased nonfatal stroke
- decreased CV death
- decreased all mortality
- decreased hospitalizations for HF

FDA label for CV benefit for canagliflozin and empagliflozin only
SGLT2 Inhibitors

Mechanism of action

- osmotic diuresis (modulation of cardio-renal axis)
- weight loss
- decrease arterial stiffness
- decrease left ventricular afterload
- decrease in blood pressure

Renal benefits include

- decrease in renal disease progression
- delaying dialysis
SGLT2 Inhibitors

Adverse effects

- genital mycotic infections especially in women and uncircumcised men
- increase risk of UTIs
- normoglycemic DKA (especially in clinical trials with type 1 DM)
- increased amputation risk (canagliflozin)
- increased bone fractures (canagliflozin)
Medication Therapies in Type 2 Diabetes: Non-Insulin Injected

• GLP-1 Inhibitors
  – Exenatide* (Byetta), exenatide XR (Bydureon), liraglutide (Victoza), dulaglutide (Trulicity), lixisenatide (Adlyxin), semaglutide (Ozempic)

• Amylin synthetic
  – Pramlintide (Symlin)
Medication Therapies in Type 2 Diabetes: Non-Insulin Injected

Combination Therapies

Xultophy- degludec + liraglutide (Tresiba + Victoza)

iGlarLixi/Soliqua- glargine + lixisenatide (Lantus + Adlyxin)
GLP-1 Agonist

Liraglutide, semaglutide and dulaglutide have been shown to have cardio protective effects.

- decrease major CV events
- decrease CV death
- decrease all mortality

Appear to have an anti-atherothrombotic effect

Decrease blood pressure and weight without hypoglycemia risk.
Metabolic Defects in Type 2 Diabetes

Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet

- Decreased Incretin Effect
- Impaired Insulin Secretion
- Islet β-cell
- Increased Lipolysis
- Increased Glucagon Secretion
- Increased HGP
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

Metabolic Defects in Type 2 Diabetes

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

2. ↓ Incretin effect

3. α-cell defect

4. Adipose
   - Increased lipolysis

5. Muscle
   - Decreased peripheral muscle uptake

6. Liver
   - Increased glucose production

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

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

FINAL COMMON DENOMINATOR

HYPERGLYCEMIA

INSULIN RESISTANCE

UC Irvine Health
Sites of Action in Type 2 Diabetes

- **Insulin secretion**
  - ↑ Sulfonpyrethas
  - ↑ Meglitinides
  - ↑ Incretins

- **Glucagon secretion**
  - ↓ Incretins
  - ↓ Amylin

- **GI**
  - Incretins
  - α-glycosidase inhibitors
  - Amylin
  - Bile acid sequestrant

- **Hepatic glucose output**
  - ↓ Metformin
  - ↓ Thiazolidinediones

- **Lipotoxicity**
  - Thiazolidinediones
  - Salicylates

- **Hyperglycemia**

- **Appetite control**
  - Incretins
  - Amylin

- **Glucose reabsorption**
  - SGLT2 inhibitors

- **Glucose uptake and utilization**
  - ↑ Thiazolidinediones
  - ↑ Metformin

UC Irvine Health
Medications in Diabetes

Insulin Options
The Goal of Insulin Therapy: Attempt to Mimic Normal Pancreatic Function
Patterns of Glucose, Insulin, and Glucagon After Oral Glucose in Type 2 Diabetes

Insulin Therapy Options

- Rapid acting- lispro*(Humalog/Admelog), lispro U200*, aspart* (Novolog), glulisine (Apidra),* inhaled regular(Afrezza) , aspart (Fiasp)
- Short acting- regular*, regular U500
- Intermediate acting- NPH*
- Long acting- glargine* (Lantus/Basaglar), glargine U300 (Toujeo), detemir*(Levemir), degludec (Tresiba), degludec U 200 (Trisiba)
Insulin Therapy Options

Combination insulins

70/30 mix*- 70%NPH and 30%Regular (Humulin/Novolin)
75/25 mix*- 75%NPL and 25% lispro (Humalog)
50/50 mix* - 50% NPL and 50% lispro (Humalog)
70/30* analog mix - 70% insulin aspart (Novolog) protamine and 30% aspart
70/30 mix-70% degludec and 30% aspart (Ryzodeg)
# Human Insulins and Analogues Typical Times of Action

<table>
<thead>
<tr>
<th>Insulin Preparations</th>
<th>Onset of Action</th>
<th>Peak</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspart, glulisine, lispro</td>
<td>~15 minutes</td>
<td>1–2 hours</td>
<td>4–6 hours</td>
</tr>
<tr>
<td>Afrezza Inhaled regular</td>
<td>0-1 minute</td>
<td>20-30 minutes</td>
<td>90 minutes</td>
</tr>
<tr>
<td>Human regular</td>
<td>30–60 minutes</td>
<td>2–4 hours</td>
<td>6–8 hours</td>
</tr>
<tr>
<td>Human NPH</td>
<td>2–4 hours</td>
<td>4–10 hours</td>
<td>12–20 hours</td>
</tr>
<tr>
<td>Glargine, Detemir, etc</td>
<td>2–4 hours</td>
<td>Flat</td>
<td>12-42 hours</td>
</tr>
</tbody>
</table>
Pharmacokinetics of Insulin Products

Figure 2. Approximate Pharmacokinetic Profiles of Human Insulin and Insulin Analogues.
The relative duration of action of the various forms of insulin is shown. The duration will vary widely both between and within persons.

Basal Bolus Regimen with Glargine and Lispro
Twice-daily Split-mixed Regimens
Summary of Pathophysiology

- **Type 1 diabetes**
  - The main abnormality is insulin deficiency

- **Type 2 diabetes**
  - Both insulin deficiency and insulin resistance contribute

- **Glucotoxicity and lipotoxicity**
  - Poor metabolic control worsens insulin deficiency and insulin resistance
**Medication & Meal Planning**

**BASAL MEDICATIONS**
- Consistent carbohydrate
- Calorie control for weight management
- Small, frequent meals may be of benefit
- Heart healthy foods
- Glycemic index/Glycemic load guide

**BOLUS MEDICATIONS**
- Match carbohydrate load to medication action
- Calorie control as needed for weight management
- Carbohydrate counting
- Heart healthy foods
- Higher risk for hypoglycemia on oral meds when meals are skipped
Exercise Safety

- Obtain medical clearance
- Wear appropriate clothing and footwear
- Monitor blood glucose before, during and after exercise
- BG target is 90-180mg/dL. No exercise if BG >275/300mg/dL
- Wear medical ID
- Know how to adjust insulin(s) for exercise
- Carry a fast-acting carbohydrate source
Insulin Delivery

Syringes, Pens & Pumps
Insulin Delivery Options

- vial and syringe
- inhaled
- insulin pen devices
- insulin pump
- IV insulin
Self-Management Tools

The Apps Store
Chronic Disease Tools
Barriers to Diabetes Self Management
Much more than a patient

A chronic disease “patient” is a patient for an average of four 15-minute doctor visits a year...

...and a person living with chronic disease for the other 8,759 hours of the year
Barriers to Diabetes Management

• Clinical inertia by healthcare providers
• Patient’s access to transportation, cost of DM supplies/medications/education.
• Lack of healthy food choices in the neighborhood
• Limited literacy/health literacy
• Long standing diabetes with very old lifestyle habits
Health Disparities

• Diabetes care is often deficient in minority populations

• Diabetes complications (renal disease, amputation, neuropathy) are higher in minority populations

• Limited access to health care services

• Health myths and misconceptions
Health Disparities

- Fewer medical visits
- Underdiagnosis
- Lower rates of recommended monitoring tests for diabetes
- Decrease in optimal health
Diabetes Education at Least Once
Seen by a Physician at Least Once a Year
Care Indicators for California Guideline Therapy

• Annual dilated eye exam 59.7%
• Annual foot exam 62.9%
• 2 or more A1c tests 63.9%
• Flu vaccine 50.6%
• Pneumococcal vaccine 46.6%
• At least one MD/DO/NP visit/year 79.3%
Self Care Behaviors: California

- Daily blood glucose monitoring 42.7%
- Self foot exam 49%
- Attended at least 1 diabetes self management class 64.5% (6% of Medicare beneficiaries use their DSMT benefit)
- Smoking 13.1%
- Physical Inactivity 28%
- Obese 48.2%
- Cardiovascular risk awareness (HTN=58.9% Chol=56.7%)
Models of Success

2% reduction in A1c with...

• Adequate health care interventions and diabetes education that is culturally sensitive provided by a multidisciplinary team at the provider’s location.

Reimbursement is available for DSME, DPP and MNT. (MediCare, MediCal and commercial)
Resources

Free patient education materials in multiple languages

www.diabetes.org

www.eatright.org

www.nih.gov

www.cdc.gov

www.diabeteseducator.org
## Resources

<table>
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<th>Resource</th>
<th>Website</th>
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</thead>
<tbody>
<tr>
<td>Dietary Guidelines for Americans</td>
<td><a href="http://www.dietaryguidelines.gov">www.dietaryguidelines.gov</a></td>
</tr>
<tr>
<td>My Pyramid Tracker</td>
<td><a href="http://www.mypyramidtracker.gov">www.mypyramidtracker.gov</a></td>
</tr>
<tr>
<td>Nutrition</td>
<td><a href="http://www.eatright.org">www.eatright.org</a></td>
</tr>
<tr>
<td>Healthy People</td>
<td><a href="http://www.healthypeople.gov">www.healthypeople.gov</a></td>
</tr>
<tr>
<td>Aim for a Healthy Weight</td>
<td><a href="http://www.nhlbi.nih.gov">www.nhlbi.nih.gov</a></td>
</tr>
<tr>
<td>National Weight Registry</td>
<td><a href="http://www.nwcr.ws">www.nwcr.ws</a></td>
</tr>
<tr>
<td>Calorie, Fat, Carbohydrate Counter</td>
<td><a href="http://www.calorieking.com">www.calorieking.com</a></td>
</tr>
<tr>
<td>U.S. National Physical Activity Plan</td>
<td><a href="http://www.physicalactivityplan.org">www.physicalactivityplan.org</a></td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention</td>
<td><a href="http://www.cdc.gov/obesity">www.cdc.gov/obesity</a></td>
</tr>
<tr>
<td>Diagnosis and Management of Obesity. 2013</td>
<td><a href="http://www.aafp.org">www.aafp.org</a></td>
</tr>
</tbody>
</table>
References


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American Association of Clinical Endocrinologists, AACE, www.aace.com
THANK YOU