DIABETES: Don’t Sugarcoat It

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Learning Objectives

1. Describe and differentiate type 1 and type 2 diabetes

2. Identify the criteria required for diagnosis of diabetes and the analytical methods used in the clinical laboratory

3. Discuss blood glucose monitoring, insulin administration, and medications used in managing diabetes
Outline

Clinical Presentation
- Normal glucose handling
- Diabetes
  - Type 1 vs Type 2
  - Symptoms

Diagnosis
- Blood glucose
- HbA1c
- Oral glucose tolerance test

Treatment/Monitoring
- Glucose monitors
- Insulin therapy
- Oral medications used for T2D
Case Study: Patient Presentation

Patient: Cookie
• 59-year-old man
• Height: 5’7”
• Weight: 220 lbs
• BMI: 34.5 kg/m²

Patient complaints
• Poor diet

Patient history
• Sedentary lifestyle
• Father with Type 2 diabetes
How Our Body Gets Energy

Carbohydrates in food we eat

During digestion carbohydrates broken down into glucose

Glucose is converted to energy used by most cells in the body
Pancreatic Islet Coordinates Glucose Homeostasis

- **Exocrine tissue** (digestive enzymes)
- **Endocrine tissue** (hormones)

- **α-cell**
  - Glucagon → simulate glycogenolysis/gluconeogenesis → blood glucose ↑

- **β-cell**
  - Insulin → stimulates glucose uptake → blood glucose ↓

- **δ-cell**

- **ε-cell**

- **PP-cell**
Glucose Regulation

Glucose stored and/or used in organs

Glucose in the blood

LIVER

MUSCLE

Normal level of glucose in the blood

Glucose

STOMACH

PANCREAS

Insulin
Dysfunctional Glucose Regulation

- Glucose release from the STOMACH
- Insulin release from the PANCREAS
- Metabolic processes in the LIVER and MUSCLE
- Increased level of glucose in the blood
What is Diabetes Mellitus

Group of metabolic disorders characterized by high levels of sugar in the blood

- **TYPE 1 DIABETES (T1D)**
  Beta cells that produce insulin are destroyed, leading to insulin deficiency

- **TYPE 2 DIABETES (T2D)**
  Body produces insulin, but can’t use it well

- **GESTATIONAL DIABETES (GDM)**
  Transient condition during pregnancy

High blood glucose = Hyperglycemia
Diabetes Mellitus Epidemiology

DIABETES IS ON THE RISE

422 MILLION adults have diabetes

THAT’S 1 PERSON IN 11

3.7 MILLION deaths due to diabetes and high blood glucose

1.5 MILLION deaths caused by diabetes

www.who.int/diabetes/global-report  *Statistics from 2016 global report*
Diabetes in the US

*Statistics from 2017 report*

2.3x greater health care costs for Americans with diabetes

$327B annual cost of diagnosed diabetes in America

34M More than 34 million Americans have diabetes

By county

- less than average: 0-6%
- national average: 7-10%
- above average: 11% or higher

88M More than 88 million Americans have prediabetes

https://www.diabetes.org/resources/statistics/cost-diabetes
Type 1 vs Type 2 Diabetes

Type 1
• “Juvenile” diabetes
• Insulin-dependent diabetes mellitus (IDDM)
• Autoimmune destruction of insulin secreting beta cells
  • Cannot be prevented
• Requires insulin therapy
• 5 – 10 % of all cases

Type 2
• Tends to develop at an older age, but increasingly common in adolescence
• Occurs due to insulin resistance and progressive loss of insulin secretion
• Can be prevented with lifestyle changes
• Managed with diet/exercise and/or oral medications or insulin
• 90% cases
Blood Glucose in Diabetes

Type 1 Diabetes

Insulin deficient

Increased level of glucose in the blood

Less glucose being stored and/or used

LIVER

MUSCLE
Symptoms of Diabetes

Complications of Uncontrolled Diabetes

**Acute Complications**
- Diabetic ketoacidosis (DKA)
  - Type 1 Diabetes
- Hyperosmolar Hyperglycemic State (HHS)
  - Type 2 Diabetes
- Hypoglycemia

**Chronic Complications**
- Microvascular
- Macrovascular

Possible coma and death
Complications of Uncontrolled Diabetes

Eye damage and blindness
Kidney damage
Nerve damage
Poor circulation to the limbs

http://diabetescontrol.info/microvascular-complications-of-diabetes/
Case Study: Cookies Symptoms

Laboratory Methods for Diagnosis

1. Hb A₁c
2. Glucose
3. Oral Glucose Tolerance Test (OGTT)

https://www.diabetes.org/diabetescare
Hemoglobin (Hb) $A_{1c}$

- “Glycated hemoglobin”

https://www.cigna.com/individuals-families/health-wellness/hw/hemoglobin-tp10337  
https://www.aboutkidshealth.ca/article?contentid=1754&language=english
Hb A₁c

• Test used in diagnosis and monitoring of diabetics
  • Average blood glucose level over previous 3 months

Calculated Estimated Average Glucose (mg/dL) = 28.7 x HbA₁c – 46.7

<table>
<thead>
<tr>
<th>A₁c (%)</th>
<th>eAG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>97</td>
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<tr>
<td>6</td>
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<tr>
<td>11</td>
<td>269</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
</tr>
</tbody>
</table>

Nathan et. al. Diabetes Care 2008;31:1473-1478
Hb A\textsubscript{1c}

**Advantages**

- Assess average glucose over a 3 month window
- Not dependent on fasting
- Greater preanalytical stability
- Less daily variation
- Useful for monitoring patients

**Limitations**

- Cost
- Lower sensitivity
- Indirect measure
  - Interpretation depends on RBCs having a normal life span
  - Impacted by age, race/ethnicity, HIV treatment, anemia, and hemoglobinopathies

Image: https://www.wellthy.care/hba1c-test-diabetes-blood-sugar/
Laboratory Methods to Measure Hb $A_1c$

Charge Differences

- Ion-Exchange High Performance Liquid Chromatography (HPLC)*
- Capillary Electrophoresis

Structural Differences

- Immunoassay*
- Affinity Chromatography

*Most common methods

Hb A\textsubscript{1c} by HPLC

- Separates Hb A1c and other Hb based on charge differences
Hb A\textsubscript{1c} by Capillary Electrophoresis

- Silica capillary
- High voltage applied to separate molecules by electrophoretic mobility (size and charge)
- Detection at 415 nm – specific to hemoglobin

HbA1c Assay Interferences:
http://www.ngsp.org/interf.asp

Image: sebia.com
Methods for Diagnosis

1. Hb A\textsubscript{1c}
2. Glucose
3. Oral Glucose Tolerance Test (OGTT)
Measurement of Glucose

• Specimen
  • Plasma: Grey top tube (sodium fluoride) – inhibits glycolysis
  • Whole blood (glucometers)
  • Interstitial fluid (continuous glucose monitors)
  • Urine – dipstick; screening only

https://www.laboratoryalliance.com/tests/display/503
https://www.medicalnewstoday.com/articles/317466
Sample Type Matters

- Capillary/whole blood vs. plasma
- Reference intervals differ based on sample type
Methods for Measurement of Glucose

• Enzymatic methods with photometry or amperometry detection
  • Hexokinase – reference method
  • Glucose oxidase

Hexokinase Method

• Most automated analyzers

Glucose + ATP $\xrightarrow{\text{HEXOKINASE}}$ Glucose-6-phosphate + ADP

Glucose-6-phosphate $\xrightarrow{\text{GLUC-6-PD}}$ 6-Phosphogluconate

NAD $\xrightarrow{\text{NADH}}$ NADH

NADH production measured photometrically at 340 nm

Glucose concentration is directly proportional to change in absorbance
Glucose Oxidase Method

- Lab-based and point-of-care systems
- Photometric or Amperometric detection

Glucose concentration is directly proportional to intensity of color

Laboratory Methods for Diagnosis

1. Hb A\textsubscript{1c}
2. Glucose
3. Oral Glucose Tolerance Test (OGTT)
Oral Glucose Tolerance Test (OGTT)
OGTT

**Advantages**

- High sensitivity (81-93%)
- Detects early impairment

**Limitations**

- Time consuming
- Extensive pre-test fasting
- Influenced by stress, illness, and medications
- Improper handling or storage of sample can skew results
Diagnosis of Diabetes

A1C
- ≥ 6.5%: DIABETES
- 5.7 – 6.4%: PREDIABETES
- < 5.7%: NORMAL

Fasting Plasma Glucose
- ≥ 126 mg/dL: DIABETES
- 100-125 mg/dL: PREDIABETES
- < 100 mg/dL: NORMAL

Oral Glucose Tolerance Test
- 2-hour measurement
- Random glucose ≥ 200 mg/dL

Diagnosis should include ≥ 2 abnormal results

https://www.diabetes.org/diabetescare
## Case Study: Patient Testing

<table>
<thead>
<tr>
<th>Chart/Lab Table format results</th>
<th>Patient Result</th>
<th>RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb A&lt;sub&gt;1C&lt;/sub&gt;</td>
<td>8.0% H</td>
<td>&lt; 5.7%</td>
</tr>
<tr>
<td>Fasting Plasma Glucose</td>
<td>154 mg/dL H</td>
<td>&lt; 100 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>152 mg/dL</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>97 mg/dL</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>35 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

- Diagnosis = Type 2 Diabetes
Treatments
Treatments

**INSULIN**
All people with T1D need to take insulin every day. Only some people with T2D require this medication.

**MEDICATIONS**
Individuals with T2D may take a daily cocktail of one or more medications (and sometimes insulin) to help keep blood sugar in a healthy range.

**DIET AND EXERCISE**
Although T1D cannot be managed with lifestyle changes, eating a healthy diet and regularly exercising can provide big benefits to those with T2D.

**SELF-MONITORING**
Treatment starts at home where blood glucose should be tested everyday (multiple times per day). Based on the glucose levels patients can adjust what and when to eat. For T1D this also helps determines how much insulin to inject.
Insulin

- Insulin administered daily to keep blood glucose levels close to target range, without causing hypoglycemia

Syringe/pens

Inhaler

Insulin Pump

https://www.mhealth.org/sitecore/content/Fairview/Home/Patient-Education/

https://www.aboutkidshealth.ca/Article?contentid=1733&language=English
Medications for T2D

Liver
- Decrease glucose production
  - Metformin (pioglitazone)

Kidney
- Inhibit glucose reabsorption in the kidney
  - Sodium-glucose co-transporter 2 (SGLT2) inhibitors (e.g., dapagliflozin)

Gut
- Enhance levels of active incretin hormones
  - Dipeptidyl peptidase 4 (DPP-4) inhibitors (e.g., sitagliptin)

Pancreatic beta cells
- Increase insulin secretion
  - Sulphonylureas (e.g., glibenclamide)
  - Non-SU secretagogues (e.g., repaglinide, nateglinide)

Muscle and adipose tissue
- Increase glucose uptake
  - (Increased insulin sensitivity)
  - Metformin (pioglitazone)

Ways to reduce hyperglycaemia
Glucose Monitoring

Glucometer

Continuous Glucose Monitor

Glucometer image: https://en.wikipedia.org/wiki/OneTouch_Ultra

CGM image: https://drneetadeshpande.com/CGMS.php
Diet and Exercise

Healthy Diet
• Reduce sugars, starches, and fatty foods

Exercise Regularly
• Reduce insulin resistance

Weight Loss
• Can aid in reduction of blood glucose

Images: https://stock.adobe.com/tr/search
Case Study: Treatment Plan

• Referred to Diabetes clinic for patient education
• Worked with nutritionist to improve diet
• Discussed importance of exercise
• Learned how to use glucose monitor
Case Study: 3-month Follow-up

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Result at diagnosis</th>
<th>Current result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>220 lbs</td>
<td>222 lbs</td>
</tr>
<tr>
<td>Hb A$_{1C}$</td>
<td>8.0% H</td>
<td>8.2% H</td>
</tr>
</tbody>
</table>

• Self-management not enough
• Prescribed 500 mg metformin 2x per day with meals

Liver: Decrease glucose production

Muscle and adipose tissue: Increased glucose uptake (increased insulin sensitivity) Metformin (pioglitazone)
Conclusions

• Diabetes is a group of metabolic disorders characterized by high levels of sugar in the blood

• Diagnosis requires measurement of fasting plasma glucose, Hb A$_{1c}$, and/or OGTT

• Treatment requires regular glucose monitoring and may include insulin or therapeutics designed to increase insulin secretion or decrease hepatic glucose production
  
  • Diet and lifestyle choices are also very important factors in successful treatment
THANK YOU...
Case Study

• Patient: Cookie

18: suggest larger diagram of HPLC system
   - do you want to include cations? show competition?
27: Dress up slide now that you split it
40: picture credits
31: boxes are difficult to see - such a great slide and important information - would not want to lose the audience
   - what are the most common treatments, why, and are multiple given simultaneously?

35: diagnosis of type 2 diabetes based on age? anything more to confirm that it is type 2 and not type 1?
good job of using reminders

Other ideas:
- reduction in risk by weight loss and diet e.g., X% reduction in body mass leads to a reduced risk of T2D of X%
- individual cost and national cost of DM