Diabetes and Obesity: The Evolution of the Egregious 11

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Disclosures
Susan Cornell and Stuart T. Haines declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Which of the following is the fundamental problem that leads to hyperglycemia in type 2 diabetes?

- Abnormal Gut Microbiota
- Beta-cell dysfunction
- Insulin resistance
- Liver dysfunction

Target Audience: Pharmacists
ACPE#: 0202-0000-17-078-LD4-P
Activity Type: Application-based
According to the B-centric model for diabetes, all of the following contribute to the development of diabetes except:

- Auto-antibodies
- Free Fatty Acids
- Sugary foods
- Systemic inflammation

Which of the following medications addresses multiple pathways that contribute to hyperglycemia in patients with type 2 diabetes?

- Acarbose
- Empagliflozin
- Glimeperide
- Insulin degludec

Which of the following medications is most likely to be well-tolerated and requires the least monitoring?

- Canagliflozin
- Linagliptin
- Insulin aspart
- Pioglitazone

Objectives

- Discuss the pathogenesis and natural history of diabetes progression.
- Describe the normal regulation of blood glucose and insulin secretion with respect to the egregious 11 of diabetes pathophysiology.
- Identify differences between pre-diabetes, type 1, type 1.5 and type 2 diabetes mellitus with respect to the egregious 11.
- Formulate treatment plans that target the patient’s unique, beta-cell centric profile.


29.1 million with Diabetes
86 million with Prediabetes


Type 2 Diabetes with Severe Insulin Resistance Due to Obesity and Physical Inactivity

- Obesity
- Diagnosed with Diabetes
- Physically inactive
Insulin Resistance

- Major defect in individuals with pre-diabetes/T2DM
- Reduced biological response to insulin
- Closely associated with obesity
- Associated with cardiovascular risk
- Type 1 diabetes patients can be insulin resistant as well

How many system “defects” lead to diabetes?
What causes Insulin Resistance (IR)?

It’s Time for: Phamily Feud

Pancreatic Beta Cell
Liver

What are the 11 defects that lead to diabetes?

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3/25/2017
What are the 11 defects that lead to diabetes?

1. Peripheral tissue
2. Stomach/Small intestine
3. Pancreatic alpha cell
4. Kidney
5. Adipose tissue/fat

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1. Peripheral tissue
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What are the 11 defects that lead to diabetes?

1. Colon/Biome
2. Incretin effect
3. Immune dysregulation
4. Inflammation
5. 10
6. 11

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What are the 11 defects that lead to diabetes?

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Defect Count</th>
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<tbody>
<tr>
<td>Pancreatic Beta Cell</td>
<td>15</td>
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<tr>
<td>Liver</td>
<td>12</td>
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<tr>
<td>Peripheral tissue</td>
<td>12</td>
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<tr>
<td>Stomach/Small intestine</td>
<td>11</td>
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<tr>
<td>Pancreatic alpha cell</td>
<td>10</td>
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<tr>
<td>Kidney</td>
<td>10</td>
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<tr>
<td>Adipose tissue/fat</td>
<td>9</td>
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<tr>
<td>Brain</td>
<td>8</td>
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<tr>
<td>Colon/Biome</td>
<td>5</td>
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<tr>
<td>Incretin effect</td>
<td>4</td>
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<td>Immune dysregulation</td>
<td>4</td>
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<tr>
<td>Inflammation</td>
<td>4</td>
</tr>
<tr>
<td>Kidney</td>
<td>10</td>
</tr>
</tbody>
</table>

Pathways that lead to B-cell Dysfunction

- The following contribute to b-cell dysfunction
  - Insulin resistant organs
    - Liver
    - Muscle
    - Adipose tissue
  - Other organs
    - Brain
    - Colon
    - Immune system

B-Cell Loss is Responsible for Hyperglucagonemia in T2DM

- Beta cells outnumber alpha cells in healthy subjects.
- Alpha cell mass is not altered by T2DM
- As T2DM progresses, the ratio of alpha to beta cells increases.

The Role of the Kidney in Diabetes

- As blood glucose increases the kidney reabsorbs the glucose, so it will not spill into the urine.
  - A1c of 6.5% -- renal threshold is ~ 205 mg/dl
  - A1c of 9% -- renal threshold is ~ 260 mg/dl

Gut Microbiome

- Gut microbiome role in digestion
- Strengthens immune system
- Prevents infections
- Antibiotic use may increase risk of T2DM
  - Kill good bacteria -- allowing bad bacteria to dominate GI tract
  - Alters nutrient absorption and metabolism
- Pre/Pro-biotics may address this mediator of hyperglycemia
Environmental Factors

- Endocrine disruptors
- Food additives
- Abnormal gut biome
- Ingested advanced glycation end products
- Concern that some environmental factors may alter genotype in reproductive cells
- Diabetes genetic inheritance

Inflammation in Diabetes

- Systemic low grade inflammation in:
  - Type 1
  - Type 1.5
  - Type 2
- Endoplasmic stress due to increased metabolic demand for insulin.
- Early studies show incretin hormones exert anti-inflammatory affects.
  - E.g. DDP-4i may delay progression of type 1.5

Classification and Treatment

- Leaders in Diabetes are calling for a change in how diabetes is classified
  - Focus should be B-cell centric
    - Opposed to Type 1, Type 1.5, Type 2, monogenic, etc.
- Abnormal or genetically pre-disposed B-cells lead to:
  - Insulin resistance
  - Susceptibility to environmental influences
  - Immune dysregulation
  - Inflammation

B-cell Centric Model

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 1.5</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Auto-antibodies</td>
<td>C-peptide</td>
</tr>
<tr>
<td>HLA-DQ</td>
<td>Naive T-cells</td>
<td>Insulin treatment</td>
</tr>
<tr>
<td>T-cell</td>
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</tbody>
</table>

Let’s Play JEOPARDY

<table>
<thead>
<tr>
<th>What’s Your Type?</th>
<th>Get A Plan Stan</th>
<th>Minions to the Rescue!</th>
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<tr>
<td>100</td>
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<td>200</td>
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<td>200</td>
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<td>300</td>
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Final Jeopardy
What’s Your Type?  100

The Answer is:
A form of diabetes where hyperglycemia is primarily the result of an autoimmune destruction of beta-cells but patients are often misclassified because oral agents often work for 6 months or longer.

What is ....
a) Type 1 diabetes
b) Type 2 diabetes
c) LADA
d) MODY

---

Diabetes Classification

• Current Diabetes Classification System – 4 big buckets
  • Type 1 DM (beta-cell destruction; auto-immune disease)
  • Pre-diabetes & Type 2 DM (multifactorial pathophysiology)
  • Gestational DM (multifactorial pathophysiology)
  • Other (specific genetic abnormalities; endocrinopathies; drug-induced)
• LADA = Latent Autoimmune Diabetes in Adults
• MODY = Maturity Onset Diabetes of the Young


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What’s Your Type?  200

The Answer is:
A form of diabetes where hyperglycemia is due to beta-cell dysfunction coupled with other derangements such as diminished L-cell function, elevated free fatty acids, and low serum ghrelin.

What is ....
a) Type 1 diabetes
b) Type 2 diabetes
c) LADA
d) MODY

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Diabetes Pathophysiology

• L-cell
  • Intestinal lumen; secrete incretin hormone GLP-1
  • Signals β-cell in pancreas
• Lipid metabolism
  • Energy metabolism alerted; free fatty acids are released
  • Toxic effect on β-cell
• Leptin and Ghrelin
  • Regulate hunger and obesity
  • Paradoxical findings in DM type 2


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What’s Your Type?  300

The Answer is:
A form of diabetes where patients don’t secrete amylin. The number of new cases in children less than 15 years old is expected to double in the next 15 years.

What is ....
a) Type 1 diabetes
b) Type 2 diabetes
c) LADA
d) MODY

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Diabetes Pathophysiology

• α-cells secrete glucagon — regulates gluconeogenesis in liver
• β-cells co-secrete insulin and amylin — regulates glucose uptake from gut and into cells
• Type 1 diabetes and LADA – destruction and relatively rapid β-cell loss
• Type 2 diabetes – dysregulation and slowly progressive β-cell loss
• MODY – genetic defects which influence insulin secretion or resistance; β-cell loss not a common feature

Fajans SS and Bell GD. Diabetes Care 2011; 34: 1878-84.
Get a Plan Stan 100

The Answer is:
A medication that is considered one of the best choices for overweight patients with type 2 diabetes who have coronary artery disease because it can reduce cardiovascular events and mortality.

What is ....

a) alogliptin
b) empagliflozin
c) glimeperide
d) rapaglinide

Get a Plan Stan 200

The Answer is:
A medication that should be avoided in patients with heart failure or a T-score less than – 1.5.

What is ....

a) canagliflozin
b) liraglutide
c) pioglitazone
d) repaglinide

Get a Plan Stan 300

The Answer is:
A medication that should be used in adult patients with an ICA titer > 12 JDF units.

What is ....

a) dapagliflozin (or similar)
b) exenatide (or similar)
c) metformin (or similar)
d) insulin detemir (or similar)

Antidiabetes Drugs & CV Disease

• Cardiovascular disease is the leading cause of death in patients with diabetes (regardless of type)
• In patients with type 2 diabetes, some drugs appear to influence cardiovascular outcomes:
  • Metformin (UKPDS-34)
  • Empagliflozin (EMPA-REG Outcome)
  • Liraglutide (LEADER)
• Unanswered questions: Class effect? Mechanism?

Antidiabetes Drugs & ADRs

• Insulin and insulin secretagogues – hypoglycemia and weight gain
• Metformin – GI symptoms and lactic acidosis in high risk patients
• Thiazolidenediones – weight gain, peripheral edema, new onset heart failure, osteoporosis, and bladder cancer?
• DPP4 Inhibitors – well tolerated, upper respiratory infections?
• SGLT2 Inhibitors - genitourinary tract infections, electrolytes, euglycemia DKA
• GLP-1 receptor agonists – Nausea/vomiting, pancreatitis?

Lab Tests to Consider

• Baseline glycemic control (plasma glucose + A1c)
• C-peptide, Glutamic Acid Decarboxylase Autoantibodies (Anti-GAD), Islet Cell Cytoplasmic Autoantibodies (ICA), Insulin Autoantibodies (IAA)
• Renal Function (SCr, BUN, eGFR)
Minions to the Rescue! 100

The Answer is:
A combination of antidiabetes medications that will likely result in significant weight loss - an important goal in a patient with type 2 diabetes who is obese.

What is....
- Acarbose and glipizide
- Bromocriptine and rosiglitazone
- Canagliflozin and dulaglutide
- Metformin and sitagliptin

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Minions to the Rescue! 200

The Answer is:
Beyond a quarterly A1c check, this medication would require the least follow-up for monitoring of adverse effects or dose adjustments.

What is....
- Insulin degludec
- Linagliptin
- Liraglutide
- Metformin

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Minions to the Rescue! 300

The Answer is:
A combination of antidiabetic medications that is more likely to preserve beta-cell mass and function for longer periods of time in patients with type 2 diabetes.

What is....
- Acarbose and bromocriptine
- Metformin and glipizide
- Pioglitazone and exenatide
- Saxagliptin and colesevelam

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Weight and Antidiabetes Meds

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Impact on Weight</th>
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<tbody>
<tr>
<td>Human Insulins</td>
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<tr>
<td>Sulfonylureas</td>
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<tr>
<td>Thiazolidinediones</td>
<td>▲▲ (plus insulin ▲▲▲▲)</td>
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<tr>
<td>Meglitinides</td>
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<tr>
<td>Biguanides (metformin)</td>
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<tr>
<td>Dipeptidylpeptidase-4 (DPP4) inhibitors</td>
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<tr>
<td>α-glucosidase inhibitors</td>
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<td>Biguanides (metformin)</td>
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<td>Bromocromipine</td>
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<td>Amylin analogues</td>
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<tr>
<td>Sodium-glucose co-transporter 2 (SGLT2) inhibitors</td>
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<tr>
<td>Glucagon-like peptide-1 (GLP-1) agonists</td>
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Tolerance and Follow-up

- Hypoglycemia – insulin and insulin secretagogues
- Gastrointestinal effects – metformin, GLP-1 receptor agonists, bromocromipine, colesevelam, α-glucosidase inhibitors, amylin
- Dose titration or adjustments – insulin, metformin, sulfonylureas, GLP-1 agonists, bromocromipine, amylin
- Well tolerated, limited follow-up required – DPP4 inhibitors

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Diabetes Clinical Trial at Texas Diabetes Institute

- Triple therapy at diagnosis
- GLP-1 agonist + TZD + metformin
- Results show durable and stable reduction in A1c for 4+ years
- Study is ongoing

“We don’t treat breast cancer with 1 drug, wait for it to fail, and hope we have a good outcome.”

Ralph DeFronzo, MD
Take-Aways

Take 68.3 seconds to share with your “neighbor” your 2 “take-aways” from today’s session

Summary

• Diabetes is often the result of multiple defects involving more than one organ system
• Our current classification system does not account for the diversity of defects that may be present
• The treatment approach should be individualized and match the pathophysiology
• Combination therapy (diet, physical activity, and medications) is always necessary to achieve optimal health outcomes

Which of the following is the fundamental problem that leads to hyperglycemia in type 2 diabetes?

- Abnormal Gut Microbiota
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According to the B-centric model for diabetes, all of the following contribute to the development of diabetes except:

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