Diabetes Strategies for the 21st Century: Pathogenesis of Diabetes

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___ Yes  Name: CME activity for Diabetes Strategies for the 21st Century

___ No
National Diabetes Statistics

- Fast Facts on Diabetes
- 29.1 million people or 9.3% of the U.S. population have diabetes.
- Diagnosed
- 21.0 million people
- Undiagnosed
- 8.1 million people
  - (27.8% of people with diabetes are undiagnosed).

CDC, 2014

Pre Diabetes Statistics

- Pre diabetes among people aged 20 years or older, United States, 2012
  - 86 million Americans age 20 and older had prediabetes:
    - this is up from 79 million in 2010.

Case #1

A 47-year-old black man is admitted to the ICU with hyperglycemia. He presented to the ED with polyuria, polydipsia, and abdominal pain. He has no history of diabetes and has been treated only for hypertension and gout in the past. His mother, maternal aunt, and maternal grandmother all developed T2DM in their 60s but none of his siblings or children are affected. He has a history of binge drinking but has not had alcohol recently. He has lost 10-20 lbs over the last 2 months.

On PE, he is in no acute distress. Height is 79 in and weight is 277 lbs, BMI 31.2. His RR is 18 breaths/min, and HR is 92 beats/min. Findings on fundoscopic and abdominal examinations are normal. There are no signs of neuropathy.
**Case #1 continued**

Lab test results (sample drawn at hospital admission):
Glucose 617 mg/dL
Sodium 139 mEq/L
Potassium 3.3 mEq/L
Chloride 97 mEq/L
Bicarbonate 20 mEq/L
Serum acetone 2+
Aspartate aminotransferase 77 U/L
Alanine aminotransferase 67 U/L
BUN 53 mg/dL
Creatinine 1.7 mg/dL
TG 1798 mg/dL
Venous pH 7.28
Hemoglobin A1C 10.7%
Lipase 190 U/L (nl: 10-73)
Amylase 55 U/L (nl: 26-102)

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1. Autoimmune diabetes
2. Type 2 diabetes mellitus
3. Maturity-onset diabetes of the young type 1
4. Alcoholic ketoacidosis
5. Pancreatitis

ERB 2014
Case #2

A 46-year-old man presents for advice on treatment of type 2 diabetes mellitus (DM). He has been treated with metformin for 4 years since having an elevated blood glucose detected on a preoperative evaluation. His glucose control has varied and a sulfonylurea was added last year when his HbA1c increased to >8%. However, he gained 5 kg with this treatment and stopped the drug after 6 months. He is otherwise healthy and his only medications are metformin and lisinoprel. On exam, his BMI is 33 kg/m2 and his blood pressure is 138/84 mm Hg. Repeat HbA1c is 8.4%.

Question #2

Which of the following treatments is the best option for this man?

1.) Repaglinide
2.) Sitagliptin
3.) Liraglutide
4.) Pioglitazone
5.) Insulin glargine
Case #3

• A 41 yo man with no notable medical history presents to the ED with a 3 month history of fatigue, an unintentional 5-lb weight loss, and a 3 week history of mild polyuria and nocturia. His family history includes T2DM in a maternal aunt. His BP is 126/88 mm Hg, weight is 163 lb (74.1 kg), and BMI is 27 kg/m2. His PE findings are unremarkable with no localizing signs of infection.

• Lab test results:
  • Random glucose=288 mg/dL
  • A1C 8.8%
  • Creatinine 0.7 mg/dL
  • U/A: 3+ protein, no WBCs
  • CBC: normal
  • ABG: not done

Case #3 Continued

• You see him 1 month later, while he is taking metformin, 500 mg tid. You review the following additional lab test results:
  • Random serum glucose: 223 mg/dL
  • C-peptide 1.2 ng/mL
  • Glutamic acid decarboxylase antibodies, positive in moderate titer
  • Insulin autoantibodies, negative
  • Review of his twice-daily SMBG log reveals most values in the range of the high 100s to low 200s mg/dL, with an average of 189 mg/dL.

ERB 2015
Question # 3

Which of the following is the best next step to manage this patient’s glycemia?

A. Increase the metformin dosage
B. Add a sulfonylurea
C. Increase the metformin dosage and add a sulfonylurea
D. Add a once-weekly glucagonlike peptide 1 (GLP-1) agonist
E. Start insulin

Incidence of Type 1 Diabetes

- Incidence increasing by 3.4% per year
- 50% of patients diagnosed before age 20 years
- 50% of patients diagnosed after age 20 years
  - Often mistaken for type 2 diabetes—may make up 10% to 30% of individuals diagnosed with type 2 diabetes
  - Oral agents ineffective; insulin therapy required
  - Autoimmune process slower and possibly different
  - Can usually be confirmed by islet cell antibodies (ICA), glutamic acid decarboxylase antibodies (GADA), insulin antibodies (IAA), and/or insulinoma-2–associated antibodies (IA-2A)

Naik RG, Palmer JP. Curr Opin Endocrinol Diabetes. 1997;4:308-315
**Differential Diagnosis Type 1 and Type 2 Diabetes**

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual clinical course</td>
<td>Insulin-dependent</td>
<td>Initially non insulin-dependent</td>
</tr>
<tr>
<td>Usual age of onset</td>
<td>&lt;20 years (but ~50% over 20 years)</td>
<td>&gt;40 years but increasingly earlier</td>
</tr>
<tr>
<td>Body weight</td>
<td>Usually lean</td>
<td>Usually obese</td>
</tr>
<tr>
<td>Clinical onset</td>
<td>Often acute</td>
<td>Subtle, slow</td>
</tr>
<tr>
<td>Ketosis-prone</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Family history</td>
<td>≤15% with 1° relative</td>
<td>Common</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Predominantly white</td>
<td>More common in minorities</td>
</tr>
<tr>
<td>Frequency of HLA-DR3, DR4, DQB1*0201, *0302</td>
<td>Increased</td>
<td>Not increased</td>
</tr>
<tr>
<td>Islet autoantibodies (GADA, ICA, IA-2A, IAA)</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

**Type 2 Diabetes: Pathogenesis in a Nutshell**

- A failure of the β-cell to compensate adequately for insulin resistance
- Obesity is the most common cause of insulin resistance
- Most obese people have adequate β-cell compensation and therefore do not get diabetes
- There is a genetic predisposition to β-cell failure

Type 2 Diabetes: Pathogenesis in a Nutshell (cont.)

- Type 2 diabetes is a PROGRESSIVE disease
  - β-cell dysfunction first leads to impaired glucose tolerance, which progresses in some individuals to type 2 diabetes
  - β-cell dysfunction starts long before blood glucose rises and worsens after diabetes develops
- Hyperglycemia may cause additional defects in insulin secretion and insulin action (glucotoxicity)

Kahn SE. J Clin Endocrinol Metab. 2001;86:4047-4058.

Natural History of Type 2 Diabetes

Adapted from Ramlo-Halsted BA, Edelman SV. Prim Care. 1999;26:771-789
Insulin Resistance in IGT and Type 2 Diabetes

Glucose disposal rate (mg/m²/min)

IGT=impaired glucose tolerance

Treating Insulin Resistance Reduces Incidence of Type 2 Diabetes

12.1% annual incidence rate
55% risk reduction
5.4% annual incidence rate
Treating Insulin Resistance Preserves β-Cell Function

Placebo (n=40)

Troglitazone (n=44)

Etiology of Type 2 Diabetes
Impaired Insulin Secretion and Insulin Resistance

Genes and environment

Impaired insulin secretion

Insulin resistance

Impaired glucose tolerance

Type 2 diabetes

Progressive hyperglycemia and high free fatty acids

Data from women who completed TRIPD without diabetes; post-trial testing was done an average of 8 months after study medications were stopped.

Hyperglycemia In Type 2 Diabetes

Insulin Resistance: Receptor And Postreceptor Defects

Increased Glucose Production  Insufficient Glucose Disposal

Liver  ➔ Glucose  ➔ Peripheral Tissues (skeletal muscle)

Pancreas  ✗

Impaired Insulin Secretion


Eight Mechanisms Which Lead to Hyperglycemia in Type 2 Diabetes

Figure 1: Eight mechanisms that lead to hyperglycemia in patients with type 2 diabetes. The brain has neurotransmitter dysfunction. The liver produces excess glucose; Beta cells in the pancreas secrete less insulin. Alpha cells in the pancreas secrete excess glucagon. Skeletal muscles have decreased glucose uptake. The kidneys reabsorb more glucose; Adipose tissue has increased lipolysis; Intestines have decreased incretin effect. This is also known as the "Omnius Ordin." Adapted from DeFronzo 2009.

Illustration by Kaitlin Jones
Beta Cells of Pancreas Secrete Less Insulin

Decline of β-Cell Function in the UKPDS Illustrates Progressive Nature of Diabetes

HOMA=homeostasis model assessment
UKPDS. Diabetes. 1995;44:1249-1258
Altered β-Cell Mass and Function in Islets From Subjects With Type 2 Diabetes

Decreased Skeletal Muscle Glucose Uptake
Insulin Resistance and Skeletal Muscle

Insulin mediated glucose clearance rates in leg skeletal muscle

Increased Lipolysis by Adipose Tissue
**Mechanism of Glucotoxicity and Lipotoxicity**

The Glucosamine Hypothesis

- Glucose
- FFA

- Other pathways
- Increased glucosamine
- Other pathways

- Impaired insulin secretion from β-cell
- Insulin resistance in muscle and fat

FFA=free fatty acid


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**High FFA Levels Cause Peripheral and Hepatic Insulin Resistance**

Glucose Measurements During High Insulin Levels

- Glucose uptake or output (mg/dL fat-free mass/min)

- Insulin
- Insulin + fat infusion

- *P<0.05

FFA=free fatty acid

Increased Glucagon by Alpha Cells

Glucagon in Type 2 Diabetes

Figure 1 Main contributors to hyperglycemia in Type 2 diabetes mellitus. AGE: advanced glycation end products.

Godoy-Matos Diabetology & Metabolic Syndrome 2014, 6:91
http://www.dmsjournal.com/content/6/1/91
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

Impaired Regulation of Postprandial Glucose

- In impaired glucose tolerance or diabetes, glucose regulation is impaired by
  - Delayed and reduced insulin secretion
  - Lack of suppression of glucagon
  - Hepatic and peripheral insulin resistance

- Postprandial hyperglycemia results
Increased Hepatic Glucose Production

**Increased Hepatic Glucose Output Correlates With Fasting Plasma Glucose**

Conclusion: FBG<140 did not trigger HGP increase, but increase in HGP was seen FBG>140. HGP does not play early role in fasting hyperglycemia of T2DM.

DeFronzo RA. *Diabetes.* 1988;37:667-687
Neurotransmitter Dysfunction

Energy Balance:
Afferent and Efferent Signals

- Afferent Signals That Increase Appetite
  - GI tract
  - Endocrine system
  - Peripheral nervous system
  - Central nervous system

- Afferent Signals That Decrease Appetite
  - GI tract
  - Endocrine system
  - Adipose tissue
  - Peripheral nervous system
  - Central nervous system

Hypothalamus
Efferent signals
Energy intake and expenditure

Substances That Promote Positive Energy Balance (Weight Gain)

- Neuropeptide Y
- Melanin-concentrating hormone
- Agouti-related peptide
- Ghrelin
- Galanin
- Orexin A and B
- Dynorphin
- β-Endorphin
- Norepinephrine
- Epinephrine
- Opioids
- Growth hormone–releasing hormone
- Somatostatin
- Androgen
- Progesterone


Substances That Promote Negative Energy Balance (Weight Loss)

- Leptin
- Peptide YY3-36
- Ciliary neurotrophic factor
- Insulin
- α-Melanocyte–stimulating hormone
- Glucagon-like peptide-I
- Urocortin
- Neurtotensin
- Corticotropin-releasing hormone (CRTH)
- Cocaine-amphetamine-regulated peptide (CART)
- Bombesin
- Cholecystokinin
- Enterostatin
- Serotonin
- Dopamine

### Assessing Risk: BMI and Waist Circumference‡

<table>
<thead>
<tr>
<th>Disease Risk*</th>
<th>BMI (kg/m²)</th>
<th>Obesity class</th>
<th>Men &lt;102 cm (&lt;40 in)</th>
<th>Women &lt;88 cm (&lt;35 in)</th>
<th>&gt;102 cm (&gt;40 in)</th>
<th>&gt;88 cm (&gt;35 in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td></td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 – 24.9</td>
<td></td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 – 29.9</td>
<td></td>
<td>Increased</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Obesity</td>
<td>30.0 – 34.9</td>
<td>I</td>
<td>High</td>
<td>Very high</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td></td>
<td>35.0 – 39.9</td>
<td>II</td>
<td>Very high</td>
<td>Very high</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Extreme obesity</td>
<td>≥40</td>
<td>III</td>
<td>Extremely high</td>
<td>Extremely high</td>
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*Relative risk for type 2 diabetes, hypertension, and cardiovascular disease, compared with normal weight and waist circumference.

†Measured at top of iliac crest.

© 2003 PHS

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Decreased Incretin Effect
Exenatide: Effect on the β-Cell

- Synthetic peptide, which mimics actions of glucagon-like protein 1 (GLP-1)
  - enhances glucose-dependent insulin secretion
  - suppresses inappropriately elevated glucagon secretion
  - delays gastric emptying
- Effect on β-cells
  - Animals, cell-line studies
    - increase expression of key β-cell function genes
    - increase insulin biosynthesis and processing
    - augment β-cell mass (increase neogenesis and proliferation, reduce apoptosis)
  - Human trials
    - treated patients demonstrate improved proinsulin:insulin ratio
    - robust insulin secretion to meal stimulus despite lower fasting and postprandial glucose concentrations

Increased Glucose Reabsorption
Kidney

- Kidneys reabsorb filtered glucose via SGLTs
  - <1% of glucose excreted in urine
- SGLT2 reabsorbs >90% of filtered glucose
  - SGLT1 absorbs remaining glucose
- SGLT in the diabetic kidney
  - Animal models of type 2 diabetes show increased expression of SGLT1 and SGLT2 mRNA with increases in renal glucose transporter expression and activity
  - Data suggest reabsorption of glucose from proximal tubule becomes maladaptive in diabetes

SGLT2 inhibitors block reabsorption of filtered glucose in kidneys; leads to glucosuria, improved glycemic control

SGLTs: membrane proteins responsible for transporting glucose across brush-border membrane of proximal renal tubule and across intestinal epithelium

SGLT1:
- located in distal segments

SGLT2:
- predominantly expressed in earlier segments of proximal tubule

mRNA=messenger ribonucleic acid; SGLT=sodium-glucose co-transporter

Glucose Reabsorption and the Kidney


Classification of Diabetes

Ketosis-prone Type 2 Diabetes

- “Flatbush diabetes”, area in city of Brooklyn, NY where this type of DM first described
- Commonly nonwhite and overweight or obese with acute defects in insulin secretion and no islet cell autoantibodies
- Following treatment, some insulin secretory capacity is recovered
- Initially Rx with insulin, then Rx as T2DM with oral agents +/- diet


Latent Autoimmune Diabetes in Adults (LADA)

- Heterogeneous group
- On spectrum of insulin deficiency between type 1 and type 2 diabetes
- Those with high titers of GAD65 antibodies have lower body mass index and less endogenous insulin secretion
- Anti-GAD antibodies (or ICA) indicate need for insulin and increase risk for developing ketoacidosis

Up to Date. Classification of diabetes mellitus and genetic diabetic syndromes, 2017.
Maturity Onset Diabetes of the Young (MODY)

- Heterogeneous disorder characterized by non-insulin dependent diabetes diagnosed at a young age (<25 years)
- Autosomal dominant transmission
- Lack of autoantibodies
- Generally do not develop DKA
- Most common form of monogenic diabetes, accounting for 2-5% diabetes
- Misclassified as having either type 1 or type 2 diabetes
- Rx: sulfonylureas

Up to Date. Classification of diabetes mellitus and genetic diabetic syndromes, 2017.

Genetic Abnormalities of MODY

- Hepatocyte nuclear factor -4-alpha (was called MODY1) (<10%)
  - Rx: SU
- Glucokinase gene (was called MODY 2) (15-31%)
  - Rx: mild DM, no meds
- Hepatocyte nuclear factor-1-alpha (was called MODY 3) (52-65%)
  - Rx: SU, glinides
- Insulin promoter factor 1 (was called MODY 4) (rare)
- Hepatocyte nuclear factor-1-beta (was called MODY 5) (rare)
- Neurogenic differentiation factor-1 (was called MODY 6) (rare)

Note: Some MODYs need insulin
Fajans & Bell, Diab Care, 34, 2011: 1878-1994
Up to Date. Classification of diabetes mellitus and genetic diabetic syndromes, 2017.
Genetic Syndromes Associated with Diabetes Mellitus

Box 2
Other genetic syndromes (that may be associated with diabetes mellitus)

- Down syndrome (T1DM and T2DM)
- Klinefelter syndrome
- Turner syndrome
- Huntington chorea
- Friedreich ataxia
- Prader-Willi syndrome
- Myotonic dystrophy
- Porphyria
- Laurence-Moon-Biedl syndrome
- Others

Others


Drug Associated Diabetes Mellitus

Box 1
Drug-associated diabetes mellitus

- Glucocorticoids
- Diazoxide
- Calcineurin/mammalian targets of rapamycin inhibitors
- Atypical antipsychotics
- Antiretroviral agents
- Thiazide diuretics
- Nicotinic acid
- Statins
- β-adrenergic agonists
- Others

Newer Atypical Antipsychotics

• Side effects: weight gain
• Diabetogenic effects: glucose dysregulation
  – Clozapine
  – Olanzapine
  – Risperidone
  – Quetiapine
  – Aripiprazole
• Increased risk of T2DM, metabolic syndrome and dyslipidemia
• Rare cases of DKA


Case #1

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ERB 2014
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B. Add a sulfonylurea  
C. Increase the metformin dosage and add a sulfonylurea  
D. Add a once-weekly glucagonlike peptide 1 (GLP-1) agonist  
E. Start insulin

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
Summary of Pathophysiology

• Basal hyperglycemia
  – Basal insulin levels and hepatic response mainly determine fasting plasma glucose

• Postprandial hyperglycemia
  – Early insulin release, glucagon suppression, and hepatic and muscle responses to insulin response determine postprandial glucose