PATHOGENESIS OF DIABETES MELLITUS

Harsha Karanchi, MD, FACE
Division of Endocrinology, Diabetes and Metabolic Diseases
Medical University of South Carolina
Charleston, SC

Disclosures

- No conflicts of interest
Learning Objectives

- Review the pathogenesis of diabetes mellitus
- Describe and differentiate type 1 and type 2 diabetes
- State diagnostic criteria

<table>
<thead>
<tr>
<th>Classification of Diabetes mellitus</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 diabetes</strong></td>
<td></td>
</tr>
<tr>
<td>A. Immune mediated</td>
<td></td>
</tr>
<tr>
<td>B. Idiopathic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>β-cell destruction leading to absolute insulin deficiency</td>
</tr>
<tr>
<td><strong>Type 2 diabetes</strong></td>
<td>Insulin resistance +/- insulin deficiency</td>
</tr>
<tr>
<td><strong>Gestational diabetes mellitus (GDM)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Other specific types</strong></td>
<td></td>
</tr>
<tr>
<td>A. Genetic defects of β-cell function</td>
<td></td>
</tr>
<tr>
<td>B. Genetic defects in insulin action</td>
<td></td>
</tr>
<tr>
<td>C. Diseases of exocrine pancreas</td>
<td></td>
</tr>
<tr>
<td>D. Endocrinopathies</td>
<td></td>
</tr>
<tr>
<td>E. Drug or chemical induced</td>
<td></td>
</tr>
<tr>
<td>F. Infections</td>
<td></td>
</tr>
<tr>
<td>G. Uncommon forms of immune-mediated diabetes</td>
<td></td>
</tr>
<tr>
<td>H. Other genetic syndromes associated with diabetes</td>
<td></td>
</tr>
</tbody>
</table>
**Differential Diagnosis of 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><strong>Usual clinical course</strong></td>
<td>Insulin-dependent</td>
<td>Initially non-insulin-dependent</td>
</tr>
<tr>
<td><strong>Usual age of onset</strong></td>
<td>&lt;20 years (but ~50% over 20 years)</td>
<td>&gt;40 years but increasingly earlier</td>
</tr>
<tr>
<td><strong>Body weight</strong></td>
<td>Often lean but ~50% overweight or obese</td>
<td>Usually obese</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Often acute</td>
<td>Subtle, slow</td>
</tr>
<tr>
<td><strong>Ketosis prone</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>≤15% with 1st-degree relative</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Frequency of HLA</strong></td>
<td>Increased</td>
<td>Not increased</td>
</tr>
<tr>
<td><strong>Islet autoantibodies</strong></td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

GADA, glutamic acid decarboxylase; HLA, human leukocyte antigen; IAA, autoantibodies to insulin; IA-2A, tyrosine phosphatase insulinoma antigen; ZnT8A, zinc transporter 8.

*Needs to be refined for nonwhite population groups.


---

**Type 1 Diabetes Pathophysiology**

- **β-cell destruction**
  - Usually leading to absolute insulin deficiency
- **Immune mediated**
- **Idiopathic**

CD8, cluster of differentiation 8; FasL, Fas ligand; IFN-γ, interferon-γ; IL-1, interleukin-1; MHC, major histocompatibility complex; NO, nitric oxide; TNF-α, tumor necrosis factor α.

Time course of type 1 diabetes mellitus

Time course of the development of type 1 diabetes. Genetic markers are present from birth, immune markers first appear at the time of the environmental triggering events, and sensitive metabolic markers of deficient insulin secretion begin to appear soon after the onset of beta cell dysfunction. However, clinically evident type 1 diabetes does not occur until there has been a much greater loss of functioning beta cell mass.

Type 1 diabetes staging

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmunity</td>
<td></td>
<td>Autoimmunity</td>
<td>New-onset hyperglycemia</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td></td>
<td>Dysglycemia</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Presymptomatic</td>
<td></td>
<td>Presymptomatic</td>
<td></td>
</tr>
<tr>
<td>Diagnostic criteria</td>
<td>Multiple autoantibodies</td>
<td>Multiple autoantibodies</td>
<td>Clinical symptoms</td>
</tr>
<tr>
<td>No IGT or IFG</td>
<td></td>
<td></td>
<td>Diabetes by standard criteria</td>
</tr>
</tbody>
</table>
Immune-Mediated Diabetes (T1a Diabetes)

**β-Cell Destruction**
- Variable rate
  - Rapid in infants and children (primarily)
  - Slow in adults (primarily)

**Immune Markers**
- Islet cell autoantibodies
- Autoantibodies to insulin
- Autoantibodies to GAD (GAD65)
- Autoantibodies to the tyrosine phosphatases IA-2 and IA-2b

When fasting hyperglycemia is first detected, 85% – 90% of individuals have ≥1 autoantibody.


---

**Symptoms and Severity of T1D at Presentation**

**Presenting Symptoms**
- Polyuria: 96%
- Weight Loss: 61%
- Fatigue: 52%

**DKA at Presentation**
- Severe DKA: 9%
  - 33% with pH 7.1–7.3
  - 9% with pH < 7.1
- DKA: 42%

DKA, diabetic ketoacidosis; T1D, type 1 diabetes.
Incidence and Prevalence of Type 1 Diabetes

- T1D is the major type of diabetes in youth
  - Accounts for ≥85% of all diabetes cases in patients <20 years of age
- Incidence is increasing by 2% to 5% worldwide
- U.S. prevalence is approximately 1 in 300

Diabetes in Children and Young Adults

- In the past, diabetes in youth was almost always T1D, but more T2D is no longer “adult onset” diabetes only
- Nearly all children with diabetes diagnosed <10 years have T1D
  - Majority of non-Hispanic youth with diabetes diagnosed have T1D
- However, among US children 10-19 years at diagnosis
  - Half of African-American and Hispanic patients have T2D
  - More than half of Asian/Pacific Islanders and American Indians have T2D
Type of Diabetes in Youth by Race/Ethnicity and Etiology

SEARCH for Diabetes in Youth Study (N=2291)

Distribution of etiologic categories by race/ethnicity

- Non-autoimmune + IR
- Non-autoimmune + IS
- Autoimmune + IR
- Autoimmune + IS

AA, African American; AI, American Indian; API, Asian/Pacific Islander; IR, insulin resistant; IS, insulin sensitive; NHW, non-Hispanic white.


Worldwide Prevalence of Diabetes

Current estimated prevalence: 415 million worldwide
By 2040, 642 million people worldwide are expected to have diabetes

Prevalence of Diabetes and Prediabetes in the United States

- Undiagnosed DM
- Diagnosed DM
- Prediabetes


Prediabetes 34% of US population
Diabetes 9.4% of US population

Prevalence of Diagnosed Diabetes in Different US Ethnic and Racial Groups

US Adults ≥18 Years of Age

- Men
- Women

T2D Prevalence Parallels Prevalence of Obesity

BMI, body mass index (in kg/m²); CDC, Centers for Disease Control and Prevention; NHANES, National Health and Nutrition Examination Survey (x-axis lists last year of each survey).

*NHANES 1994 data.


Criteria for diagnosis of diabetes

Table 2.2—Criteria for the diagnosis of diabetes

<table>
<thead>
<tr>
<th>Criteria for diagnosis of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).</td>
</tr>
</tbody>
</table>

*In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.
Natural History of Type 2 Diabetes

Pathophysiology of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Role</td>
<td></td>
</tr>
<tr>
<td>Pancreatic beta cells</td>
<td>Decreased insulin secretion</td>
</tr>
<tr>
<td>Muscle</td>
<td>Inefficient glucose uptake</td>
</tr>
<tr>
<td>Liver</td>
<td>Increased endogenous glucose secretion</td>
</tr>
<tr>
<td>Contributing Role</td>
<td></td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Increased FFA production</td>
</tr>
<tr>
<td>Digestive tract</td>
<td>Decreased incretin effect</td>
</tr>
<tr>
<td>Pancreatic alpha cells</td>
<td>Increased glucagon secretion</td>
</tr>
<tr>
<td>Kidney</td>
<td>Increased glucose reabsorption</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Neurotransmitter dysfunction</td>
</tr>
</tbody>
</table>
Acute Insulin Response Is Reduced in Type 2 Diabetes

Plasma IRI (µU/ml)

Time (minutes)

20 g glucose infusion

1st
2nd phase

Normal (n=85)

Type 2 diabetes (n=160)

IRI, immunoreactive insulin.

Defective Insulin Action in Type 2 Diabetes

Leg Glucose Uptake (mg/kg leg wt per min)

Time (minutes)

P<0.01

Total Body Glucose Uptake (mg/kg • min)

T2D, type 2 diabetes.
Elevated Fasting Glucose in Type 2 Diabetes
Results From Increased HGP


The Incretin Effect Is Diminished in Type 2 Diabetes

90% of glucose
(180 L/day) (90 mg/dL) = 162 g glucose per day

10% of glucose

Normal Renal Handling of Glucose

Increased SGLT2 Protein Levels Change Glucose Reabsorption and Excretion Thresholds
Mechanism of Action of Antihyperglycemic Agents

**Pancreas**
- Decreased insulin secretion from β-cells
  - GLP1 RA, DPP4i, SU, GLN

**Muscle**
- Increased glucose uptake
  - TZD

**Adipose (fat)**
- Increased FFA production
  - TZD

**Brain**
- Neurotransmitter dysfunction
  - GLP1 RA
  - Bromocriptine

**Liver**
- Increased endogenous glucose production
  - Metformin, TZD, GLP1 RA, DPP4i

**Kidney**
- Increased glucose reabsorption
  - SGLT2i

**Digestive tract**
- Decreased incretin effect
  - GLP1 RA, AGis, Colesevelam

**The Ominous Octet**

---

DeFronzo RA. *Diabetes*. 2009;58:773-795
What about insulin secretion and action if born to DM/GDM mothers?
What about a past history of GDM?

History of GDM increases risk of DM

**FIG. 2.** Cumulative incidence of diabetes mellitus among the placebo group by history of GDM.
Diabetes prevention in women with history of GDM: Intensive life style change and Metformin give hope!!

- Adiposopathy? ADIPO-SO-what?
Adiposopathy in metabolic syndrome: adipocyte hypertrophy as opposed to adipocyte hyperplasia


Adiposopathy: decreased plasticity and abnormal distribution of adipose tissue --> Insulin Resistance

What is the personal fat threshold?

Intensive Lifestyle Intervention Effectively Prevents Progression From IGT to T2D

Diabetes Prevention Program (N=3234)

- Intensive lifestyle intervention (n=1079): 58% reduction, 4.8 per 100 Person-Years
- Metformin 850mg BID (n=1073): 31% reduction, 7.8 per 100 Person-Years
- Placebo (n=1082): 11 per 100 Person-Years

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise.

IGT, impaired glucose tolerance; T2D, type 2 diabetes.

What can we learn about the pathogenesis of type 2 diabetes mellitus from bariatric surgery outcomes?

- Bariatric surgery is an effective intervention for treating type 2 diabetes
- Improvement in metabolic control is often evident within days to weeks (weight loss independent)
- What are the underlying mechanisms?

Schematic diagram showing the major factors and pathways involved in the beneficial effects of bariatric surgeries on body weight and glucose homeostasis, with emphasis on caloric restriction and weight loss-dependent (solid lines) and –independent (broken lines) factors.
What can we learn about the pathogenesis of type 2 diabetes mellitus from bariatric surgery outcomes?

![Graph](image)

Sjostrom L, J Int Med, 2013

What do we know about the long term effects of bariatric surgery on metabolic improvement?

- Long term improvement in glucose, insulin and insulin resistance --> weight loss dependent
- Degree of weight loss is more important for long term reductions in fasting insulin and glucose than choice of bariatric surgery

![Graph](image)

Sjoholm K, Diabetes Care, 2016
• I’m sure I don’t have diabetes?? Do I??

• Can we predict T2DM earlier than detection of pre-diabetes by current criteria?
Can we predict T2DM earlier than detection of prediabetes by current criteria?

Table 2.5—Criteria defining prediabetes*
<table>
<thead>
<tr>
<th>Test Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>2-h PG during 75-g OGT</td>
<td>140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>A1C</td>
<td>5.7–6.4% (39–47 mmol/mol)</td>
</tr>
</tbody>
</table>

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.
OGTT insulin patterns: strong independent predictor of type 2 diabetes over 10 year follow up

<table>
<thead>
<tr>
<th>Pattern 1</th>
<th>Pattern 2</th>
<th>Pattern 3</th>
<th>Pattern 4</th>
<th>Pattern 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>3%</td>
<td>10%</td>
<td>15%</td>
<td>48%</td>
<td>38%</td>
</tr>
</tbody>
</table>

40% of patients with HTN and Dyslipidemia have either pre-diabetes or diabetes
Best test to screen: OGTT
90% of patients with CAD have either pre-diabetes or diabetes
Best test to screen: OGTT


◦ Are your clocks in SYNC?
Synchronizing feeding-fasting with light-dark cycle

Melkani GC, J Physiol 000.00 (2017) pp 1–10

Circadian rhythm of glucose/lipid metabolism

What about the bugs in the room?
Microbial dysbiosis can lead to
- Oxidative stress
- Inflammation
- Autoimmunity
- Obesity
Summary

- Type 1 diabetes mellitus: beta cell destruction leading to absolute insulin deficiency
- Type 2 diabetes mellitus: beta cell dysfunction in the background of insulin resistance
- Useful to think in terms of antibody status and beta cell reserve for atypical diabetes (C-peptide less than 1 ng/mL indicating insulin dependence)
- Pathophysiology of diabetes mellitus is complex
- Pre-natal and post natal factors, circadian disruption, gut microbiome all play important role
- Pre-diabetes, history of GDM: potential for greatest impact in prevention of diabetes by lifestyle change

Learning Assessment Question #1

In contrast to type 1 diabetic patients, patients with type 2 diabetes:

a) Often experience an acute onset of diabetes
b) Have an increased frequency of HLA-DR3, DR4, DQB1*0201, *0302
c) **Do not have islet autoantibodies**
d) Are often lean
Learning Assessment Question #2

Which of the following would **NOT** be considered diagnostic for diabetes?

a) FPG 130 mg/dL  
b) A1C 6.7%  
c) 2-h PG 250 mg/dL during OGTT  
d) Random PG 180 mg/dL

Learning Assessment Question #3

Which of the following is involved in the pathogenesis of type 2 diabetes?

a) Decreased FFA production by adipose tissue  
b) Increased incretin effect in the digestive tract  
c) **Increased glucose reabsorption by the kidney**  
d) Decreased glucagon secretion by pancreatic alpha cells
THANK YOU

References

- [http://outpatient.aace.com/slide-library](http://outpatient.aace.com/slide-library)
- ADA Standards of Medical Care in Diabetes – 2019, Diabetes Care 2019 Jan; 42 (Supplement 1)