Definition of Diabetes Mellitus

Diabetes mellitus consists of a group of metabolic diseases characterized by hyperglycemia resulting from defects in *insulin secretion*, *insulin action* or *both*. 
23.6 million people have diabetes

- **Diagnosed:** 17.9 million people
  - Type 1 diabetes accounts for 5% – 10%
  - Type 2 diabetes accounts for 90% – 95%
- **Undiagnosed:** 5.7 million people

Pre-Diabetes in the U.S.

- At least **57 million** adults ages 20 and older have pre-diabetes

- Pre-diabetes raises the risk for type 2 diabetes and cardiovascular disease

African Americans & Diabetes

- 3.7 million; 14.7 % of all African Americans ages 20 and older have diagnosed and undiagnosed diabetes
- African Americans are 1.8 times as likely to have diabetes as non-Hispanic whites

Hispanics/Latinos & Diabetes

- 10.4% of all Hispanics/Latinos ages 20 years and over have diabetes
- Rates vary among groups:
  - Cubans 8.2%
  - Mexican Americans 11.9%
  - Puerto Ricans 12.6%

Every 24 Hours...

- 4,384 new cases of diabetes are diagnosed
- 195 non-traumatic lower limb amputations are performed
- 128 people begin treatment for end-stage renal disease
- 50 people develop blindness
- 839 people die of diabetes or diabetes is a contributing cause of death

Derived from:
Diabetes and Cardiovascular Disease

- Heart disease and stroke
  - In 2004, heart disease was noted on 68% of diabetes-related death certificates among people aged 65 years or older.
  - In 2004, stroke was noted on 16% of diabetes-related death certificates among people aged 65 years or older.
  - Adults with diabetes have heart disease death rates about 2 to 4 times higher than adults without diabetes.
  - The risk for stroke is 2 to 4 times higher among people with diabetes.
Glucose Homeostasis

- Insulin
- Glucagon

Amylin
GLP-1

70 – 140 mg/dl

Catecholamines
Growth Hormone
Cortisol
Carbohydrate Metabolism in the Fed State

- Blood glucose concentrations rise after a meal.
- There is a subsequent release of insulin in response to the increase blood glucose.

Phase I occurs 10-20 minutes after stimulation, and is aimed at decreasing hepatic glucose production.

Phase II, continued response to long term glucose stimulation, allows glucose to enter peripheral cells.
Fasting State Carbohydrate Metabolism

- Falling blood glucose concentrations inhibit pancreatic insulin and Amylin release and stimulate the release of glucagon.
- Glucagon stimulates glycogenolysis and gluconeogenesis to ensure a minimum blood glucose concentration (at least 40 mg/dl) is maintained.
Types of Diabetes

- Type 2 Diabetes
  - Affects adults older than 40
  - More prevalent among minority populations
  - Does not require insulin
  - Associated with obesity
  - Strong familial component
Types of Diabetes

- Type 1 Diabetes
  - Usually affects white children
  - Associated with weight loss
  - Requires insulin for life
  - Associated with environmental trigger
Risk Factors for Type 2

- Medical Risk Factors
  - Pre-diabetes
  - Gestational diabetes (GDM)
  - Metabolic Syndrome
  - Lack of physical exercise
  - Obesity
Metabolic Syndrome

1. Abdominal obesity
   Men  Waist circumference greater than 40”
   Women  Waist circumference greater than 35”
2. Triglycerides  ≥ 150 mg/dl
3. HDL
   Men  < 40 mg/dl
   Women  < 50 mg/dl
4. Blood pressure  ≥ 130/85
5. Fasting glucose ≥ 100
Types of Diabetes

• Gestational Diabetes occurs during pregnancy
  • 5% to 10% of women with gestational diabetes are found to have type 2 diabetes
  • 40% to 60% women with gestational diabetes will develop diabetes in the next 5 to 10 years

Diagnostic Criteria

- Acute symptoms of diabetes plus casual plasma glucose level $\geq 200$ mg/dL
  - casual implies any time of day without regard to time since last meal.
  - The classic symptoms of diabetes include polyuria, polydipsia, polyphagia, and unexplained weight loss.

- Fasting plasma glucose $\geq 126$ mg/dL.
  (Fasting is defined as no caloric intake for at least 8 hours.

- Two-hour plasma glucose $\geq 200$ mg/dl during an oral glucose tolerance test (OGTT)

- A1C $> 6.5$%
Increased Risk

Impaired Fasting Glucose (IFG)
- diagnosed when glucose levels >100 but less than 126 mg/dL

Impaired Glucose Tolerance (IGT)
- diagnosed when 2-hour OGTT values are ≥ 140 mg/dL but less than 200 mg/dL

Elevated A1C
- 5.7 – 6.4%
Screening Recommendations

1. Testing should be considered in all adults who are overweight (BMI 25 kg/m²*) and have additional risk factors:
   - physical inactivity
   - first-degree relative with diabetes
   - members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - women who delivered a baby weighing 9 lb or were diagnosed with GDM
   - Hypertension (140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level 35 mg/dl (0.90 mmol/l) and/or a triglyceride level 250 mg/dl (2.82 mmol/l)
   - *At-risk BMI may be lower in some ethnic groups.
Screening Recommendations

- women with polycystic ovary syndrome
- A1C 5.7%, IGT, or IFG on previous testing
- other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans), history of CVD

2. In the absence of the above criteria, testing diabetes should begin at age 45 years

3. If results are normal, testing should be repeated at least at 3-year intervals, with
   - consideration of more frequent testing depending on initial results and risk
   - status.
Chronic Complications Associated with Diabetes

- Microvascular Complications
  - Retinopathy
  - Neuropathy
  - Nephropathy

- Macrovascular Complications
  - Coronary Artery Disease
  - Peripheral Vascular Disease
  - Stroke
Diabetes Prevention

- Randomized controlled trials have shown that individuals at high risk for developing diabetes (those with IFG, IGT, or both) can be given interventions that significantly decrease the rate of onset of diabetes.
- These interventions include:
  - intensive lifestyle modification programs that have been shown to be very effective (58% reduction after 3 years)
  - use of the pharmacologic agents metformin, α-glucosidase inhibitors, orlistat, and thiazolidinediones, each of which has been shown to decrease incident diabetes to various degrees.
A 35-year-old African-American man presents to you for his annual “physical exam.” He has no significant complaints but is concerned because his older sister was just diagnosed with type 2 diabetes. His father also had type 2 diabetes and died at age 54 of a myocardial infarction. He has two sons age 10 and 12, both L120% of ideal weight for their height. He is 6’0” and weighs 210 lbs (BMI 27 kg/m2); blood pressure is 138/88 mm Hg.

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>210 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40 mg/dL</td>
</tr>
<tr>
<td>LDL-C</td>
<td>140 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>96 mg/dL</td>
</tr>
</tbody>
</table>
Quick Review

A patient whose fasting plasma glucose is 120 mg/dl:

A. Impaired glucose tolerance (IGT)
B. Diabetes
C. Impaired fasting glucose (IFG)
D. Increased Risk for Diabetes
E. None of the above
Quick Review

A patient whose A1C is 6.8%:

A. Impaired glucose tolerance (IGT)
B. Diabetes
C. Impaired fasting glucose (IFG)
D. Increased Risk for Diabetes
E. None of the above
Quick Review

A patient who has a casual blood glucose of 165 mg/dl:

A. Impaired glucose tolerance (IGT)
B. Diabetes
C. Impaired fasting glucose (IFG)
D. Increased Risk for Diabetes
E. None of the above
Therapeutic Options
Goals of Therapy

- Glycemic control (A1C < 7%)
- Weight reduction (if indicated)
- Prevention of acute complications
- Prevention or delay of chronic complications
Evidence Based Support
DCCT

The Diabetes Control Complications Trial (DCCT)

- A landmark trial designed to test the proposition that the complications of DM are related to elevation of plasma glucose concentration

- **Study Design:** Involved 1441 patients. Two groups of patients were followed long term (9 years), one treated conventionally (goal: normalization blood glucose; called the standard Tx group) and another treated intensive treatment group was clearly distinguished from the standard treatment group in terms of A1c and capillary glucose levels
DCCT: Clinically Significant Findings

Continuous relationship between A1C and microvascular complication rate:

- 10% reduction in A1C → ~35% risk reduction for retinopathy
- 10% reduction in A1C → ~25%-44% risk reduction for nephropathy
- 10% reduction in A1C → ~30% risk reduction for neuropathy
- No adverse QoL or cognitive changes with intensive treatment
Evidence Based Support

DCCT

Results

1. Normalization of glucose values was not achieved in the intensively treated cohort as a group because mean glucose were ~40% above normal limits

2. ~60% reduction in risk between the intensive group and the standard group in retinopathy, nephropathy, and neuropathy

3. The benefit of the intensive therapy resulted in a delay in the onset and a major slowing of the progression of these three complications

4. The benefits of intensive therapy were seen in all categories of subjects, regardless of age, sex, or duration of disease

5. Intensively treated patients had a threefold greater risk of hypoglycemia than patients in the control group
Evidence Based Support
UKPD

- Involved over 5000 patients with newly diagnosed type 2 diabetes
- Patients were followed for an average of 10 years to determine:
  - Whether intensive use of pharmacological therapy to lower blood glucose would result in clinical benefits
  - Whether the use of various sulfonylurea drugs, the biguanide drug Metformin, or insulin have specific therapeutic advantages or disadvantages.
  - In addition patients who were hypertensive were randomized to “tight” or “less tight” blood pressure control to ascertain the benefits of lowering BP and to ascertain whether the use of ACE inhibitor (captopril) or beta-blocker (atenolol) offered therapeutic advantages or disadvantages
1. The UKPDS results establish that retinopathy, nephropathy, and possibly neuropathy are benefited by lowering blood glucose levels in type 2 diabetes with intensive therapy, which achieved a median A1c of 7% compared to conventional therapy of 7.8%.

2. Data showed a continuous relationship between the risks of microvascular complications and glycemia, such that for every percentage point decrease in A1c, there was a 35% reduction of risk of complications.

3. The results demonstrate that the risks of complications can be significantly lowered even in the range of hyperglycemia where A1c levels are <8.0%.
Evidence Based Support
UKPD

Results

4. There was no evidence of any glycemic threshold for any of the microvascular complications above normal glucose levels

5. There was a 25% reduction in diabetes-related deaths associated with every percentage point decrease in A1c.

6. The study showed that lowering blood pressure to a mean 144/82 mmHg significantly reduced strokes, diabetes-related deaths, heart failure, microvascular complication, and visual loss
The ACCORD and ADVANCE Trials: Implications for Patients with Type 2 Diabetes

Interventions that produced improvements in microvascular measures did not produce improvements in patient-important outcomes.

Summary and Comment by Harlan M. Krumholz, MD, SM

Dr. Krumholz is the author of “Redefining Quality — Implications of Recent Clinical Trials” in the same issue of the New England Journal of Medicine as the cited articles.
Background

• In patients with diabetes, high glycated hemoglobin (HbA1c) levels are associated with elevated risks for cardiovascular events and death.

• Some, but not all, studies have shown that lowering HbA1c levels reduces cardiovascular risk, and these data have been used to support current guidelines that recommend a target HbA1c level of ≤7.0%.

• To further investigate the effect of tight glucose control on cardiovascular outcomes in high-risk patients with type 2 diabetes, two studies were conducted: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial.
The Research

• In the ACCORD trial, 10,251 type 2 diabetic patients (mean age, 62; 38% women) were randomized to receive intensive glucose-lowering therapy (target HbA1c, <6.0%) or standard therapy (target HbA1c, 7.0%–7.9%).

• The primary outcome was a composite of nonfatal MI, nonfatal stroke, and cardiovascular-related death.

• The glucose-control arm of the 2x2 factorial design study was discontinued after 3.5 years of follow-up because of a greater number of deaths among patients receiving intensive therapy than among those receiving standard therapy (257 vs. 203; hazard ratio [HR], 1.22; P=0.04) (JW Cardiol Feb 13 2008).
The Research

• Within 4 months after randomization, median HbA1c levels decreased more in the intensive-therapy group (from 8.1% to 6.7%) than in the standard-therapy group (from 8.1% to 7.5%); at 1 year, median HbA1c levels had stabilized (at 6.4% and 7.5%, respectively).

• Thiazolidinediones were used by 92% of patients in the intensive-therapy group versus 58% of those in the standard-therapy group; the use of other glucose-lowering treatments was also more common in the intensive-therapy group.

• The primary outcome occurred in 6.9% of patients in the intensive-therapy group and in 7.2% of those in the standard-therapy group (HR, 0.90; P=0.16), but hypoglycemia was more common among intensive-therapy patients (10.5% vs. 3.5%; P<0.001).
The Research

• The higher mortality rate associated with intensive therapy could not be explained by severe hypoglycemia, differences in drug use, or weight change.
• Microvascular events were not reported.
The Research

• In the ADVANCE trial, 11,140 type 2 diabetic patients (mean age, 66; 43% women) were randomized to intensive therapy (target HbA1c, <6.5%) or standard therapy (target HbA1c defined by local guidelines).

• The primary outcomes, redefined during the study, were a composite of major macrovascular events (nonfatal MI, nonfatal stroke, or cardiovascular-related death) as well as separate and joint assessments of major microvascular events (nephropathy and retinopathy).
The Research

• Mean HbA1c levels at study’s end (median follow-up, 5.0 years) decreased more in the intensive-therapy group (7.5% to 6.5%) than in the standard-therapy group (7.5% to 7.3%).

• Again, both thiazolidinediones and other treatments were used by a higher proportion of intensive-therapy patients than standard-therapy patients (17% vs. 11%).

• Macrovascular events occurred at a lower rate in patients receiving intensive therapy (10.0% vs. 10.6%; HR, 0.94; P=0.3), as did microvascular events (9.4% vs. 10.9%; HR, 0.86; P=0.01).

• Mortality was slightly lower in the intensive-therapy group (8.9% vs. 9.6%; HR, 0.93; P=0.3).

• Severe hypoglycemia was more common among intensive-therapy patients (2.7% vs. 1.5%; HR, 1.86; P<0.001).
Comment

- These two studies, involving different strategies with different patterns of medication use, fail to support the hypothesis that tight glucose control in patients with type 2 diabetes will reduce their risk for macrovascular complications.
Does Glucose Control in Type 2 Diabetes Affect Cardiovascular Risk?

Results from another late-intervention study show no significant effect at about 6 years of follow-up.

Summary and Comment by Harlan M. Krumholz, MD, SM
Covering

The Research

- The investigators enrolled 1791 veterans (mean age, 60.4; mean years since diabetes diagnosis, 11.5) with poorly controlled type 2 diabetes (mean HbA1c level, 9.4%).
- Patients with body-mass indexes \( \geq 27 \) initially received metformin plus rosiglitazone, and those with BMI <27 initially received glimepiride plus rosiglitazone.
- Participants randomized to intensive therapy were prescribed maximal doses, and those randomized to standard therapy were prescribed half the maximal doses.
- Insulin was added for patients who did not achieve HbA1c levels <6% in the intensive-therapy group and <9% in the standard-therapy group.
- The primary outcome was time to first occurrence of a cardiovascular event.
The Research

• The median HbA1c stabilized by 6 months at 8.4% in the standard-therapy group and at 6.9% in the intensive-therapy group.

• At a median follow-up of 5.6 years, no significant benefit in the primary outcome was associated with intensive therapy (hazard ratio, 0.88; P=0.14).

• Ninety-five deaths occurred in the standard-therapy group, and 102 occurred in the intensive-therapy group (HR, 1.07; P=0.62).

• The two groups did not differ in the incidence of microvascular complications, including retinopathies, neuropathies, and nephropathies.
Comment

• Three studies have now failed to show that intensive glucose control in type 2 diabetes reduces the risk for cardiovascular events.
• Of the three, the present cohort had the highest mean HbA1c levels at baseline and after standard therapy; the mean HbA1C level achieved in the intensive-therapy group was the same as that achieved in ADVANCE and slightly higher than that achieved in ACCORD.
• The authors conclude that control of hypertension, dyslipidemia, and other cardiovascular risk factors, rather than a focus on intensive control of glucose, is the most effective preventive approach in these patients.
• Critics might wonder if treatment earlier in the course of diabetes or longer follow-up would have altered this study’s findings (JW Cardiol Oct 15 2008).
### Correlation between A1C and Average Glucose

<table>
<thead>
<tr>
<th>A1C (%)</th>
<th>Mean Plasma Glucose (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
</tr>
<tr>
<td>8</td>
<td>183</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
</tr>
<tr>
<td>11</td>
<td>269</td>
</tr>
<tr>
<td>12</td>
<td>298</td>
</tr>
</tbody>
</table>
Major Metabolic Defects in Type 2 Diabetes

- Peripheral insulin resistance in muscle and fat
- Decreased pancreatic insulin secretion
- Increased hepatic glucose output
- Decreased incretin effect

Haffner SM, et al. Diabetes Care, 1999
Sites of Action by Therapeutic Options Presently Available to Treat Type 2 Diabetes

LIVER
- Biguanides
- Thiazolidinediones

PANCREAS
- INSULIN Secretion
  - Sulfonylureas
  - Meglitinides
  - Insulin

ADIPOSE TISSUE
- Thiazolidinediones (Biguanides)

MUSCLE

PERIPHERAL GLUCOSE UPTAKE

INTESTINE
- Alpha-glucosidase inhibitors
- Biguanides
- Amylin Analogues
- GLP-1 agonist

## Management of hyperglycemia

### Tier 1: Well-validated

<table>
<thead>
<tr>
<th>Step 1: Initial therapy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Life style Intervention</td>
<td>1-2%</td>
<td>Insufficient for most</td>
</tr>
<tr>
<td>Metformin</td>
<td>1-2%</td>
<td>Weight neutral</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step2: Additional therapy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>1.5-3.5%</td>
<td>No dose limit, rapidly effective, weight gain, hypoglycemia, monitoring</td>
</tr>
</tbody>
</table>
## Management of hyperglycemia

**Tier 2: Less well-validated**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidindiniones</td>
<td>0.5-1.4</td>
<td>Improved lipid profile, potential decrease in MI (pioglitazone), fluid retention, weight gain, CHF</td>
</tr>
<tr>
<td>GLP1-agonist</td>
<td>0.5-1.0</td>
<td>Weight loss, requires 2 injections per day, expensive</td>
</tr>
</tbody>
</table>
### Management of hyperglycemia

#### Other Therapy

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Expected A1C Reduction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha glucosidase inhibitor</td>
<td>0.5-0.8%</td>
<td>Weight neutral, GI side effects</td>
</tr>
<tr>
<td>Glinides</td>
<td>0.5-1.5%</td>
<td>Rapidly effective, weight gain, hypoglycemia, expensive</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>0.5-1%</td>
<td>Requires 3 injections daily, GI side effects</td>
</tr>
<tr>
<td>DPP-4 Inhibitor</td>
<td>0.5-0.8%</td>
<td>Weight neutral</td>
</tr>
</tbody>
</table>
True or False
For Insulin therapy:

(A) Advantages: most effective, relatively inexpensive, and improved lipid profile.
(B) Disadvantages: injections, monitoring, hypoglycemia, and weight gain.
(C) Insulin therapy has beneficial effects on peripheral insulin sensitivity.
(D) Insulin plus glitazones may increase the risk of fluid retention.
(E) Insulin should only be used third line if 2 oral agents, including metformin, have failed to achieve the A1C target.
True or False
For thiazolidinediones therapy

(A) Advantages: pioglitazone increases HDL-C and lowers triglycerides.
(B) Disadvantages: two-fold increased risk of CHF and weight gain.
(C) Black-box warning for both rosiglitazone and pioglitazone for potential increased risk of MI.
(D) Increased risk for fractures.
(E) Dosage adjustment for patients with severe renal impairment
Treatment Goals and Preventive Measures for CVD: Hypertension

- Systolic blood pressure < 130 mmHg
- Diastolic blood pressure < 80 mmHg
- Therapy should be started with an ACE or ARB
- ACEI, ARBs, beta blockers, diuretics and calcium channel blockers have been shown to reduce cardiovascular disease events
Treatment Goals and Preventive Measures for CVD: Hyperlipidemia

- **Dyslipidemia**
  - **LDL** < 100 mm/dl
    - No overt CVD: reduce saturated fats and cholesterol intake; lose weight; indicated; statin therapy in those > 40yrs with other CVD risk factors who fail lifestyle changes; niacin
    - Overt CVD: statin therapy in all patients to reduce LDL level by 30-40%; LDL goal of < 70mg/dl
  - **HDL** > 40
    - Add fibrate (gemfibrozil, fenofibrate) to existing statin therapy; niacin therapy
  - **Triglycerides** <150 mg/dl
    - Combination therapy with statins and other lipid lowering agents
Treatment Goals and Preventive Measures for CVD: Hypercoagulability

- **Goal** – prevention of vascular events
  - Diabetes and Hx of CVD – Aspirin 75-162mg (secondary prevention)
  - Age > 40 with increased risk of CVD: ASA 75-162mg (primary prevention)
  - Patients aged 30-40 yrs with other CVD risk factors (smoking, ie.): consider ASA therapy
  - Less than 21 yrs: ASA therapy is not recommended
  - Severe and progressive CVD: clopidogrel + ASA
A 52-year-old African American woman with type 2 diabetes mellitus for 3 years presents to you for the first time for evaluation and treatment. Medications are metformin 1000 mg b.i.d.; pioglitazone 30 mg/qd; and glimepiride 4 mg qd. She has not seen a physician in over 12 months. She is married with 4 grown She drinks 1–2 glasses of wine on social occasions and quit smoking 1 year ago, with a previous 40 packs/year history (2 packs/day from age 22 to 51).
Conclusion

- Intensive glucose control significantly reduces microvascular complications.
- Macrovascular complications in patients with diabetes can be best prevented through the control of blood pressure, lipids, weight control, smoking cessation.
- Some antidiabetes medication can actually reduce some cardiovascular risk, however, others may increase risk.
- Treatment goals and therapeutic interventions should be individualized.