A. Diabetes: A Major Epidemic in U.S.

- 15.7 million Americans have diabetes (5.4 million are unaware of their condition)
- This represents a 41% increase from 1990 to 1999 (>798,000 new cases yearly or >2200 each day)

Clinical Impact of Diabetes
- Major cause of premature death and disability
- Leading cause of new cases of blindness in working-aged adults
- 50% of nontraumatic lower extremity amputations
- 35% of new cases of end-stage renal disease
- 2-to-4 fold increase in cardiovascular risk

Biochemistry in Health & Disease

General Features of Diabetes Mellitus

Diabetes mellitus is a chronic, metabolic disease.

It is characterized by an inability to clear glucose from the blood.

Diabetes mellitus can have many causes, and there are many complications that are associated with diabetes.

Two type of diabetes are recognized clinically -

**Type I** and **Type II**
A. Diabetes is an Inability to Clear Glucose from the Blood accompanied by overproduction of Glucose by the Liver. Diabetes can have many causes.

Glucose Tolerance Test

The oral glucose tolerance test is commonly used for the diagnosis of diabetes. It consists of determining the blood glucose level in the fasting state and at intervals of 30-60 min for 2 h or more after consuming a 100g carbohydrate meal.

In a normal individual blood glucose returns to normal levels within 2 h after ingestion of the carbohydrate meal. In the diabetic blood glucose will reach a higher level and remain elevated for longer periods of time, dependent upon the severity of the disease.

However, many factors such as stress or an infection may contribute to an abnormal glucose tolerance test. In fact, a majority of people screened for diabetes with a glucose tolerance test who have an abnormal result will not develop diabetes.

Because of the cited problems with the glucose tolerance test, elevation of the fasting glucose level is probably a more reliable indicator of diabetes.

Hyperglycemia

Glucosuria

High blood glucose and high glucose in the urine are characteristic features of diabetes.
B. Type I and II Diabetes

INITIAL EVENT
Exposure to a virus or toxin may start the process of β cell destruction in individuals with a genetic predisposition.

CLINICAL DISEASE
When the insulin secretory capacity falls below a threshold, the symptoms of Type I diabetes suddenly appear.

Type I Diabetes
(Insulin-Dependent Diabetes Mellitus)

Insulin-dependent diabetes mellitus, previously called juvenile-onset diabetes, usually appears in childhood or in the teens, but it is not limited to these patients.

Insulin is either absent or nearly absent in this disease because of defective or absent β cells in the pancreas. For a variety of reasons, mostly due to an autoimmune process, the β cells are destroyed.

An absolute deficiency in insulin results in excessive accumulation of circulating glucose and fatty acids with consequent hyperosmolarity and ketoacidosis.
Natural History Of Type 1 Diabetes

- **Putative trigger**
- **Circulating autoantibodies**
- **Cellular autoimmunity**
- **Loss of first-phase insulin response**
- **Glucose intolerance**

**Comparison of Type I and II Diabetes**

<table>
<thead>
<tr>
<th>Type 1 and Type 2 Diabetes</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Usually thin</td>
<td>• Usually thin</td>
<td></td>
</tr>
<tr>
<td>• Usually &lt; 20</td>
<td>• Usually &gt; 35</td>
<td></td>
</tr>
<tr>
<td>• Pancreas destroyed</td>
<td>• “insulin resistance”</td>
<td></td>
</tr>
<tr>
<td>• Always need insulin</td>
<td>• Pills &amp;/or insulin</td>
<td></td>
</tr>
<tr>
<td>• 10% of all diabetics</td>
<td>• 90% of all diabetics</td>
<td></td>
</tr>
</tbody>
</table>


**Usual Symptoms At The Time of Diagnosis**

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Excessive thirst</td>
<td>• None!</td>
</tr>
<tr>
<td>• Weight loss</td>
<td></td>
</tr>
<tr>
<td>• Poor wound healing</td>
<td></td>
</tr>
<tr>
<td>• Blurry vision</td>
<td></td>
</tr>
<tr>
<td>• Frequent urination</td>
<td></td>
</tr>
</tbody>
</table>
Type II Diabetes

Insulin Resistance: an increased secretion of insulin to clear the same amounts of glucose.

Eventually the $\beta$ cells of the pancreas give out and blood glucose levels rise.

Insulin Resistance vs Glucose Tolerance Test

Progression of Type II Diabetes

Insulin Resistance

Hepatic Glucose Production

Postprandial Blood Glucose

Fasting Blood Glucose

Endogenous Insulin

Microvascular Complications

Macrovascular Complications
Metabolic Pathway

Growth Factor Pathway

Insulin Receptor

Lecture 35

Prevalence of Diabetes in the U.S. As the Population Gets Older

% of Population

0 5 10 15 20 25 30 35 40 45 45-74

Age

25-40 million people with "pre-diabetes"

Diabetes

Undiagnosed Diabetes

"Pre"-Diabetes

Prevalence of Diabetes in the U.S. As the Population Gets Older

Insulin resistance

Hyperglycemia

Impaired glucose tolerance

Decline of β-cell function

Type 2 diabetes

Microvascular complications (retinopathy, nephropathy)

Macrovascular complications (cardiovascular disease)

Insulin Resistant

Metabolic Pathway

Growth Factor Pathway
Insulin Resistance

**Insulin Resistance: Causes and Associated Conditions**

- Obesity and inactivity
- Aging
- Medications
- Genetics
- Type 2 diabetes
- PCOS
- Hypertension
- Atherosclerosis
- Dyslipidemia
- Rare disorders
C. Factors Contributing to Insulin Resistance

Many factors can Lead to Insulin Resistance

Glucose Transporters

1. When insulin interacts with its receptor, vesicles move to the surface and fuse with the plasma membrane, increasing the number of glucose transporters in the plasma membrane.

2. Insulin receptor

3. Glucose transporter "stowed" within cell in membrane vesicles.

4. The smaller vesicles fuse with larger endosomes.

5. When insulin levels drop, glucose transporters are removed from the plasma membrane by endocytosis, forming small vesicles.

Liver/Muscle

Liver

Glucose Transporters

1. Glucose enters the liver.

2. Glucose is metabolized by Glucokinase.

3. G 6-P is produced.

4. Insulin Receptor

Many factors can Lead to Insulin Resistance

Insulin Receptor

Insulin Binding to the Insulin Receptor

1. Insulin binds to the Insulin Receptor

2. Insulin Receptor

3. IRS-1

4. P85

5. Akt

6. PDK1

7. PI-3-kinase

8. PIP2

9. PIP3

10. Many factors can contribute to Insulin Resistance.

Biochemistry in Health & Disease
Insulin Resistance is Associated with Obesity

Normal and Non-diabetic obese individuals show similar glucose tolerance test.

Both diabetics, independent of obesity, show an abnormal glucose tolerance test.

Glucose Tolerance Test

**A** Insulin level in blood

- Higher insulin levels are required to control blood glucose in the insulin-resistant, obese individual.
- Blood insulin rises from basal levels after each meal.

**B** Glucose level in blood

- Blood glucose is kept within the same narrow range throughout the day in both normal weight and obese individuals.

Effect of Obesity on Circulating Insulin Levels

More Insulin is needed to clear the same amount of Glucose.

Circulating Insulin
D. Overall Biological Responses Mediated by Insulin
(Review from Lecture 18)

The metabolic effects of insulin. Binding of insulin to membrane receptors stimulates the protein kinase activity of the receptor. Subsequent phosphorylation of target proteins modulates the effects indicated.

Insulin inhibits the secretion of glucagon.
## E. Metabolic Adaptations to Diabetes

### Major Tissues Involved

<table>
<thead>
<tr>
<th>Effect</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperglycemia</strong></td>
<td>↓ Glucose transport into muscle and adipocytes</td>
</tr>
<tr>
<td></td>
<td>↑ Gluconeogenesis</td>
</tr>
<tr>
<td></td>
<td>↓ Induction of pyruvate carboxylase, PEP carboxykinase,</td>
</tr>
<tr>
<td></td>
<td>fructose-1,6-bisphosphatase, and glucose-6-phosphatase unopposed by insulin</td>
</tr>
<tr>
<td></td>
<td>↑ Alanine from muscle</td>
</tr>
<tr>
<td></td>
<td>↓ Glycogen synthase activity and glycogen storage</td>
</tr>
<tr>
<td></td>
<td>↑ Phosphorylase activity</td>
</tr>
<tr>
<td></td>
<td>↓ Conversion of glucose to fatty acids</td>
</tr>
<tr>
<td></td>
<td>↑ Lipoprotein lipase and chylomicron and VLDL metabolism</td>
</tr>
<tr>
<td></td>
<td>↑ Hormone-sensitive lipase increases fatty acids in the</td>
</tr>
<tr>
<td></td>
<td>circulation that promote reesterification in liver</td>
</tr>
<tr>
<td></td>
<td>↑ Fatty acids in serum, promoting ketone body production</td>
</tr>
<tr>
<td></td>
<td>↓ Induction and activity of acetyl-CoA carboxylase and</td>
</tr>
<tr>
<td></td>
<td>↓ malonyl-CoA, allowing β-oxidation of fatty acids and</td>
</tr>
<tr>
<td></td>
<td>provision of acetyl-CoA for synthesis</td>
</tr>
<tr>
<td></td>
<td>↓ Amino acid transport into cells and ↓ protein synthesis</td>
</tr>
<tr>
<td></td>
<td>↑ Protein catabolism, providing alanine for gluconeogenesis and urea</td>
</tr>
<tr>
<td></td>
<td>synthesis</td>
</tr>
</tbody>
</table>

### Diagram

- **LIVER**
- **SKELETAL MUSCLE**
- **ADIPOSE TISSUE**
- **PANCREAS**
1. Hyperglycemia

Hyperglycemia

- Glucose transport into muscle and adipocytes
- Gluconeogenesis
  - Induction of pyruvate carboxylase, PEP carboxykinase, fructose-1,6-bisphosphatase, and glucose-6-phosphatase unopposed by insulin
  - Alanine from muscle
  - Glycogen synthase activity and glycogen storage
  - Phosphorylase activity
  - Conversion of glucose to fatty acids

Gluconeogenesis is active.

BRAIN
- Glucose

LIVER
- Amino Acids
- Pyr
- Glu
- NH₄⁺
- UREA
- ATP

BLOOD
- Amino Acids
- Protein
- FFA
- Ketone Bodies

MUSCLE
- FFA
- Ketone Bodies
- ATP

ADIPOCYTE
- FFA + Glycerol
- Triglycerides

No glucokinase - No longer takes up Glucose

No glucose transporter on surface
1. Hyperglycemia

Hyperglycemia

- Glucose transport into muscle and adipocytes
- Gluconeogenesis
- Induction of pyruvate carboxylase, PEP carboxykinase, fructose-1,6-bisphosphatase, and glucose-6-phosphatase unopposed by insulin
- Alanine from muscle
- Glycogen synthase activity and glycogen storage
- Phosphorylase activity
- Conversion of glucose to fatty acids

Glucosuria

Excess Glucose is excreted in the urine
2. Hyperlipidemia

Hyperlipidemia

- Lipoprotein lipase and chylomicron and VLDL metabolism
- Hormone-sensitive lipase increases fatty acids in the circulation that promote reesterification in liver
3. Ketosis

Ketosis

↑ Fatty acids in serum, promoting ketone body production
↓ Induction and activity of acetyl-CoA carboxylase and
↓ malonyl-CoA, allowing β-oxidation of fatty acids
and provision of acetyl-CoA for synthesis

<table>
<thead>
<tr>
<th>Ketone Body Accumulation in Diabetic Ketosis</th>
<th>Urinary excretion (mg/24 h)</th>
<th>Blood concentration (mg/100 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≤125</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Extreme ketosis (untreated diabetes)</td>
<td>5,000</td>
<td>90</td>
</tr>
</tbody>
</table>
4. Muscle Wasting

Muscle Wasting

↓ Amino acid transport into cells and ↓ protein synthesis
↑ Protein catabolism, providing alanine for gluconeogenesis and urea synthesis
**F. Glycosylation of Proteins**

**A1C Measures Glucose Levels over a 2-3 Month Period**

**GLYCOASYLATED HEMOGLOBIN, Hb\textsubscript{1c}**

A glycosylated hemoglobin, designated as Hb\textsubscript{1c}, is formed spontaneously in the red blood cell by combination of the N-terminal amino groups of the hemoglobin β chain and glucose.

The concentration of Hb\textsubscript{1c} is dependent on the concentration of glucose in the blood and in prolonged hyperglycemia may rise to 12% or more of the total hemoglobin.

Patients with diabetes will tend to have high concentrations of glucose and therefore high amounts of Hb\textsubscript{1c}.

The changes in the concentration of Hb\textsubscript{1c} can be used to follow the effectiveness of treatment for the diabetes.

Formation of hemoglobin A\textsubscript{ic} by the nonenzymatic addition of glucose (or glucose 6-phosphate) to the α-amino group of each β chain. A stable adduct is formed by an Amadori rearrangement of the aldimine to a ketimine.
Peripheral Neuropathies and Retinopathies are Complications of Diabetes

**Hyperglycemia and Sorbitol Metabolism**

Because insulin is not required for the entry of glucose into the cells of peripheral nerves, liver, kidney, placenta, and red blood cells, large amounts of glucose may enter these cells during times of hyperglycemia, as in uncontrolled diabetes.

Elevated intracellular glucose concentrations and an adequate supply of NADPH cause aldose reductase to produce a significant increase in sorbitol, which cannot pass efficiently through cell membranes and, therefore, remains trapped inside the cell.

This is exacerbated when sorbitol dehydrogenase is low as in retina, lens, kidney, and nerve cells.

As a result, sorbitol accumulates in these cells, causing strong osmotic effects and, therefore, cell swelling as a result of water retention.

Some of the pathologic alterations associated with diabetes can be attributed, in part, to this phenomenon, including cataract formation, peripheral neuropathy, and vascular problems leading to nephropathy and retinopathy.

**Microvascular Complications** (retinopathy, nephropathy)

**Macrovascular Complications** (cardiovascular disease)

- Insulin resistance
- Hyper-insulinemia
- Impaired glucose tolerance
- Decline of β-cell function
- Type 2 diabetes

- Genetics
- Obesity
- Sedentary lifestyle
- Aging

- Genetics
- Glucose toxicity
- Free fatty acid toxicity
Summary of Key Points

Type I and Type II Diabetes

Insulin Resistance

Hyperglycemia, Ketosis, Muscle Wasting

Hyperglycemia and Sorbitol

Obesity