Pathophysiology of carbohydrates metabolism. 

Diabetes mellitus.

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Carbohydrates
GI is a measure of the effects of carbohydrates on blood sugar levels. Carbohydrates that break down quickly, releasing glucose rapidly, have a high GI; carbohydrates that break down more slowly, releasing glucose more slowly and steadily, have a low GI.

For most people, foods with a low GI have significant health benefits.
Disaccharidase and Lactase deficiency syndromes

- **Increased level of osmotic molecules** (undigested CH molecules)
- Attract water and increase intestinal content
- Bacterial fermentation in colon
- **Diarrhea**

Regulation of the blood glucose level depends on liver

[Diagram of glucose regulation in the liver]

- Insulin
- Stimulates glycogen formation
- Stimulates glucose uptake by cells
- Tissue cells
- Glucose
- Liver
- Blood glucose falls to normal range
- Insulin
- Stimulates glycogen breakdown
- Glucose
- Liver
- Blood glucose rises to normal range
- Glucose
- Liver
- Stimulates glycogen breakdown
- Glucose
- Liver
- Blood glucose level (about 94 mg/dL)
- Maintenance
- Stimulates decreasing blood glucose level
- Glucose
- Liver
- Insulin
- Stimulates glycogen formation
- Stimulates glucose uptake by cells
- Tissue cells
- Glucose
- Liver
- Blood glucose falls to normal range
Islets of Langerhans contain 4 types of hormone-secreting cells

- **Alpha** cells (25%)
- **Beta** cells (60%)
- **Delta** cells (10%)
- **F** cells (PP cells) (5%)

The liver’s uptake and output of glucose and the use of glucose by peripheral tissues depend on the physiologic balance of several hormones that:

- **Lower blood glucose level** - insulin
- **Rise blood glucose level** - glucagon, adrenaline, GH, glucocorticoids...

(termed **contrainsular hormones**)

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**Endocrine pancreas**

**Glucose metabolism summary**
Insulin - structure

Mechanism of insulin secretion
Mechanism of insulin action

Glucose transporters (Class I)

<table>
<thead>
<tr>
<th>Glucose transporter</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT1</td>
<td>Widely distributed in fetal tissues. In the adult, it is expressed at highest levels in erythrocytes and also in the endothelial cells of barrier tissues such as the blood-brain barrier. However, it is responsible for the low-level of basal glucose uptake required to sustain respiration in all cells.</td>
</tr>
<tr>
<td>GLUT2</td>
<td>Expressed by renal tubular cells and small intestinal epithelial cells that transport glucose (enterocytes) and pancreatic β-cells. All three monosaccharides are transported from the intestinal mucosal cell into the portal circulation by GLUT2.</td>
</tr>
<tr>
<td>GLUT3</td>
<td>Expressed mostly in neurons (where it is believed to be the main glucose transporter isoform), and in the placenta.</td>
</tr>
<tr>
<td>GLUT4</td>
<td>Found in adipose tissues and striated muscle (skeletal muscle and cardiac muscle).</td>
</tr>
</tbody>
</table>
**Contrainsular hormones**

* Glucocorticosteroids
* Adrenocorticotropic hormone (ACTH)
* Glucagon (fast)
* Catecholamines (fast)
* Thyroid hormones ($T_3$ and $T_4$)
* Growth hormone

Peptide hormones – ↑ glycogenolysis and ↓ glycogenosynthesis
Steroid hormones - ↓ glucose utilization and ↑ insulin resistance (postreceptor)

**Plasma glucose levels**

- **Hyperglycemia**: Glucose concentration (mmol/L) 10
- **Fasting level diagnostic for diabetes**: Glucose concentration (mg/dL) 110
- **Normal (fasting)**: Glucose concentration (mmol/L) 6
- **Euglycemia**: Glucose concentration (mg/dL) 60
- **Hypoglycemia**: Glucose concentration (mmol/L) 3
- **Hypoglycemic coma**: Glucose concentration (mg/dL) 30

Renal threshold (approx. level at which glucose appears in urine): 180
**Hypoglycemia**
Decreased plasma glucose levels

* Physiologic state

* Pathologic condition
  - Decreased carbohydrates (CH) uptake
  - Altered CH metabolism in the liver
  - Defective regulation of glucose level

Symptoms and signs of hypoglycemia include:
- pallor, sweating, trembling, tachycardia,
- hunger, drowsiness, mental confusion,
- seizures and coma

**Hyperglycemia**
Increased in plasma glucose levels

* Alimentary
* High levels of contrainsular hormones
* Due to insulin deficiency or insulin resistance (Diabetes mellitus)
* Miscellaneous
  - Hyperthermia
  - Hypoxia
  - Severe pain
Diabetes mellitus is a heterogeneous primary disorder of carbohydrate metabolism with multiple etiologic factors that generally involve absolute or relative insulin deficiency or both and is characterized by metabolic disorders of carbohydrates, lipids and proteins.

Diabetes mellitus
Definition

Type I Diabetes Mellitus (former IDDM)
Type II Diabetes Mellitus (former NIDDM)
Other specific (former Secondary DM)
- Genetic defects (β-cells, insulin)
- Destructive diseases of the pancreas
- Endocrinopathies
- Drug induced (iatrogenic)
- Gestational diabetes

*American Diabetic Association 2012
In the new classification:

* Terms IDDM and NIDDM are not used
* Terms Primary and Secondary DM are not used

New classification also introduces new terms:

* impaired glucose tolerance (IGT)
* impaired fasting plasma glucose (IFG)

**Impaired fasting glucose (IFG)**

Condition in which the fasting blood glucose is elevated above what is considered normal levels (5.4 to 6.9 mmol/L) but is not high enough to be classified as diabetes mellitus. It is considered a pre-diabetic state, associated with insulin resistance.
Impaired Glucose Tolerance (IGT) is a pre-diabetic state of dysglycemia (6.8 to 11.0 mmol/L), that is associated with insulin resistance and increased risk of cardiovascular pathology.

Impaired glucose tolerance (IGT)  

- 100 million people worldwide  
- 85-90% cases are Type II  
- 17 million people in US (6.2% of population)  
- 5.9 million people are undiagnosed  
- Approximately 1 million new cases/year
Destruction of beta cells of pancreatic islets and as a consequence: absolute deficit of insulin

- A. subtype: induced by autoimmune processes
- B. subtype: idiopathic mechanism (up to now)
Absolute insulin deficiency ensues
Glucagon is present in relative excess
Individuals are prone to ketoacidosis
Insulin resistance is rare
Patients are insulin dependent

The result of beta cells destruction:

HLA and autoantibodies

HLA (histocompatibility locus antigen)
- HLA - DR3,-DR4 - background condition
- HLA - DQ-857-Asp - resistance gene
- HLA - DQ-857-Val/Ala/Ser;DQ-A52-Arg - predisposing genes
- TNFβ and hsp70(heat shock protein 70) gene polymorphism

Autoantibody:
- GADA (antibody to glutamic acid decarboxylase)- β-cell destruction early marker
- ICA (islet cell autoantibody)— specificity low
- IAA (autoantibody to insulin) — specificity low
- IA-2 (autoantibody to tyrosine phosphatases IA-2 and IA-2β) - high specificity
Pathogenesis of Type I DM

- Called **Type 1.5 DM** or slowly progressing insulin-dependent diabetes
- T cell mediated autoimmune disease
- Adult age at diagnosis (range 30-70 year)
- Lean or non-obesity
- The presence of diabetes-associated autoantibodies (IA2, ICA, GAD)
- Delay (at least half year) from diagnosis in the need for insulin therapy to manage hyperglycemia
- Having type 1DM’s predisposing genes (such as HLA-DR3, HLA-DR4, BW54, DQ-13157-NON-ASP etal)
- Often accompanied by thyroid and gastric parietal cells organ specific antibodies

LADA – characteristics
(Latent Autoimmune Diabetes in Adults)

- Called **Type 1.5 DM** or slowly progressing insulin-dependent diabetes
Diabetes Mellitus Type II
(Former Non-insulin dependent diabetes mellitus NIDDM)

- At the beginning—predominance of insulin resistance and relative deficit of insulin (normo- or hyper-insulinemia),
- Later on—combination of impaired insulin secretion and simultaneous insulin resistance (hypoinsulinemia, insulin resistance)

Diabetes Mellitus Type II characteristics

- 1. Primary disturbance:
  - ↓ biological activity of insulin
- 2. Compensatory hyperinsulinemia
  - due to ↑ concentration of blood glucose
- 3. Insulin resistance:
  - ↓ ability of insulin to inhibit production of glucose in liver → ↑ glucose production
1. Autoimmune reactions
   - development of anti-insulin antibodies
   - development of anti-insulin receptor antibodies
2. Defects in the insulin receptor at the cell surface
   a) defect in receptor processing
   b) decrease in receptor number
3. Defective signal transduction (from the receptor to the plasma of cell)
4. Postreceptor defect
5. Increased concentration of anti-insulinic hormones

Inherited and acquired influences on insulin resistance

- **Inherited**
  - Rare Mutations
    - Insulin receptor
    - Glucose transporter
    - Signaling proteins
  - Common Forms
    - Largely unidentified

- **Acquired**
  - Inactivity
  - Overeating
  - Aging
  - Medications
  - Hypoglycemia
  - Elevated FFAs
Pathogenesis of Type II DM summary

Signs and symptoms of Diabetes Mellitus

- Hyperglycemia
- Glycosuria
- Polyuria
- Polydipsia
- Polyphagia
- Weight loss
- Fatigue
- Poor wound healing
- Increased incidence of infections
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Natural History of Type II Diabetes

Insulin resistance
Glucose level
β-cell dysfunction
Insulin production

Time
Normal  Impaired glucose tolerance  Type 2 diabetes
Syndrome X (metabolic syndrome)

Frequently occurs in people suffering from visceral obesity

Characteristic features:
- insulin resistance
- compensatory hyperinsulinemia
- visceral obesity
- dyslipidemia (↑ LDL, ↑ TG, ↓ HDL)
- systemic hypertension

Increased probability of DM type 2 development

Characteristics of two main types of diabetes

<table>
<thead>
<tr>
<th></th>
<th>Type I DM</th>
<th>Type II DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of onset</td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Young(&lt;25 y, 12-14y)</td>
<td>&gt;40 years old (60-65y)</td>
</tr>
<tr>
<td>Clinical feature</td>
<td>typical and severity</td>
<td>Light or asymptomatic</td>
</tr>
<tr>
<td>Ketoacidosis</td>
<td>spontaneously</td>
<td>Usually having remote cause (infection etc)</td>
</tr>
<tr>
<td>Insulin or C-peptide release test</td>
<td>Low or Deficiency</td>
<td>peak value delay or absence</td>
</tr>
<tr>
<td>Body weight at onset</td>
<td>Normal</td>
<td>Overweight or obesity</td>
</tr>
<tr>
<td>Chronic impairment</td>
<td>Nephropathy(35%-40%-- mainly death cause)</td>
<td>Cardiovascular Disease(&gt;70%-- mainly death cause)</td>
</tr>
<tr>
<td>Treatment</td>
<td>insulin</td>
<td>Diet/Oral hypoglycemic agents/insulin</td>
</tr>
</tbody>
</table>
Glucose intolerance during pregnancy
Placental hormones contributes to insulin resistance
High risk: glycosuria, family history, marked obesity
Native Americans, African Americans, Hispanics and Pacific Islanders

Hormonal changes can cause the body to be less sensitive to the effect of insulin.
High blood sugar levels in pregnancy are dangerous for both mother and baby.
Diabetes - management

Early, long term, integrated, individualized

Diet control
Physical activity
Education
Drug therapy
Self-monitoring

HbA$_{1C}$ - ultimate goal

<table>
<thead>
<tr>
<th>HbA$_{1C}$ test score</th>
<th>MEAN BLOOD GLUCOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dL</td>
</tr>
<tr>
<td>14.0</td>
<td>380</td>
</tr>
<tr>
<td>13.0</td>
<td>350</td>
</tr>
<tr>
<td>12.0</td>
<td>315</td>
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<tr>
<td>11.0</td>
<td>290</td>
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<tr>
<td>10.0</td>
<td>250</td>
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<tr>
<td>9.0</td>
<td>215</td>
</tr>
<tr>
<td>8.0</td>
<td>190</td>
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<tr>
<td>7.0</td>
<td>150</td>
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<tr>
<td>6.0</td>
<td>115</td>
</tr>
<tr>
<td>5.0</td>
<td>80</td>
</tr>
<tr>
<td>4.0</td>
<td>50</td>
</tr>
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### Indication for insulin therapy

1. Type I DM
2. Type II DM:
   - Acute complication: HDC, DKA, LA
   - End stage of chronic complication
   - Stress
   - Pregnancy
   - SU* Failure
   - Severe weight loss
   - Cortisol therapy

### Acute complications

- Hypoglycemia
- Diabetic Ketone acidosis (DKA)
- Hyperosmal diabetic coma (HDC)
- Lactate acidosis
- Hypoglycemic coma
Chronic complications
(micro- & macrovascular)

- **Macrovascular (CAD, CVD (stroke), PVD)**
  Macrovascular disease - atherosclerotic lesion of larger arteries (coronary arteries, brain arteries, peripheral arteries)

- **Microvascular (kidney, reticular, nerve)**
  Microvascular disease - specific lesion of DM that affect capillaries and arterioles of the retina, renal glomeruli, peripheral nerves, muscles and skin
  - thickening of the capillary basement membrane

### Diabetes: Complications

**Macrovascular**
- Stroke
- Heart disease and hypertension 2-4 X increased risk
- Peripheral vascular disease
- Foot problems

**Microvascular**
- Diabetic eye disease (retinopathy and cataracts)
- Renal disease
- Erectile Dysfunction
- Peripheral Neuropathy
Chronic complications
Autonomic neuropathy

- **Cardiovascular Autonomic Neuropathy**
  - orthostatic hypotension
  - lack of normal variation in heart rate with breathing, tachycardia
- **Gastrointestinal Autonomic Neuropathy**
  - gastroparesis: nausea, bloating, vomiting
  - diarrhea: often nocturnal
- **Erectile dysfunction**
  - absent nocturnal and morning erections
  - more common than diagnosed

Disease Burden of Diabetes Mellitus

- Leading cause of blindness (12.5% of cases)
- Leading cause of ESRD (42% of cases)
- 50% of all non-traumatic amputations
- 2.5x increase risk of stroke
- 2-4x increase in cardiovascular mortality
- DM responsible for 25% of cardiac surgeries
- Mortality in DM: 70% due to Cardiovascular disease
Thank you !
Glucose sticks to the hemoglobin to make a “glycosylated hemoglobin” molecule, called hemoglobin A1C or HbA1C.

By measuring the HbA1C it can tell you how high your blood glucose has been on average over the last 8-12 weeks.

Normal range: 4%-6%
Main processes taking part in the liver:

1. extracting glucose from blood
2. synthesizing glycogen
3. performing glycogenolysis
4. performing gluconeogenesis

To a lesser extent peripheral tissues (muscle and adipocytes) use glucose for their energy needs, thus contributing to maintenance of normal blood glucose level