Pathophysiology of carbohydrates metabolism.

Diabetes mellitus.

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Carbohydrates

= Easy energy

*Whatever they say, it’s the ... energy!*
Glycemic index (GI)

- **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.

![Graph showing high GI vs. low GI foods](image)
Why the Glycemic Index matters
Digestion of carbohydrates

Dietary carbohydrates (starch, glycogen, sucrose, lactose)

Mouth → Salivary α-amylase

Polysaccharides, sucrose, lactose, and maltose

Stomach → Pancreatic α-amylase, maltase, sucrase, lactase

Small intestine → Monosaccharides

Absorption through small intestine lining → Monosaccharides in bloodstream
Absorption of monosaccharides

... unless you are **Fructose**!
What may go wrong?

- Reduced salivary $\alpha$-amylase (hyposalivation)
- Reduced pancreatic enzymes (chronic pancreatitis)
- Accelerated food passage (dumping syndrome)
- Reduced absorption area
- Hyponatriemia (Adison disease)
- Disaccharidase insufficiency - acquired or genetic (lactase deficiency – most common).
When it goes wrong?

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

Food → **Blood glucose**

- **Intake**
- **Digestion**
- **Absorption**

**Glycogen** → **Glycolysis** → **Glycogenolysis** → **Glycogen**

**Alanine** → **GNG**

**Loss (if > 10 mmol.L⁻¹)**

**Consumption** → **Storage (E)**
“I stand alone”

* **Insulin**

VS

• Glucocorticosteroids
• Adrenocorticotropic hormone
• Glucagon (fast)
• Catecholamines (fast)
• Thyroid hormones (T<sub>3</sub> and T<sub>4</sub>)
• Growth hormone

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

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*)*
Insulin responsibilities

- **Decreases blood glucose**
- Enhances cellular import of $\alpha$-AA, $\alpha$-KA, electrolytes ($K^+$)
- Induces the synthesis of anabolic enzymes
- Stimulates growth, cell division, DNA synthesis
- Anticatabolic effect (via gene transcription regulation)

NB! Glycogen synthesis $\uparrow$, Proteosynthesis $\uparrow$, Liposynthesis $\uparrow$
Hypoglycemia
Decreased plasma glucose levels

Food → Blood glucose → Consumption

> Glycolysis
> Renal diabetes
> Strenuous exercise
> Loss (if > 10 mmol.L⁻¹)

- Contrainisulatory hormones
- ÊCH intake Maldigestion/ Malabsorption
- Glycogeno-lysis
- Alanine
- Liver damage = Glucostat damage
- Glycogen
- #insulin
- GNG

Liver damage = Glucostat damage
Hypoglycemia

A list

• Physiologic state
• Pathologic condition
  • Decreased carbohydrates (CH) intake
  • Maldigestion/ Malabsorption of CH
  • Altered CH metabolism in the liver (cirrhosis, glycogenoses)
  • C2H5OH
  • Reactive hypoglycemia
  • Strenuous exercise
  • Renal diabetes (urinary loss)
  • Defective regulation of glucose level
    – Contrainsular hormones deficiency
    – Increased insulin levels (insulinomes, yatrogenic)
Hypoglycemia symptoms or when Nothing else matters ...but glucose

– Life-threatening condition
– Hunger and S-Adr activation
  • mydriasis
  • pallor
  • sweating
  • trembling
  • tachycardia
– Brain hypoenergetic shutdown
  • drowsiness, mental confusion, seizures and coma
Hyperglycemia
Increased in plasma glucose levels

Food → Blood glucose → Glycogen → Glycogenolysis → Glycogenolysis

#CH intake (postprandial)
Absorption

Glycogen

Insulin

Hyperthermia
Hypoxia
Severe pain

Contrainsulary hormones

Glycolysis

GNG

Storage (E)

Loss (if > 10 mmol.L⁻¹)

Insuline resistance

GLUT 4

Intake
Digestion
Absorption

Blood glucose

Contrainsulary hormones
Hyperglycemia

A list

• Alimentary
• High levels of contrainsular hormones
• Due to insulin deficiency or insulin resistance (Diabetes mellitus)
• Miscellaneous
  • Hyperthermia
  • Hypoxia
  • Severe pain
Diabetes mellitus
Definition

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

**New Classification**

- 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

**MODY** - maturity onset diabetes of the young

**LADA** - latent autoimmune diabetes in adults

*American Diabetic Association 2012*
Terminology key points

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)

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.
Diabetes mellitus
Epidemiology and Pessimism

• 382 mln people worldwide (2013) – 8.3% of the population (♂=♀)
• 85-90% cases are Type II
• up to 30% undiagnosed
• 1.5 mln deaths per year (8th in “serial killers” list)
KEEP CALM AND EAT CHOCOLATE
Diabetes Mellitus Type I
Former Insulin dependent diabetes mellitus (IDDM)

- Genetic predisposition (HLA DR3, DR4)
- Enteroviral infections
- Autoimmune reaction
The result of beta cells destruction:

- Absolute insulin deficiency ensues
- Glucagon is present in relative excess
- Individuals are prone to ketoacidosis
- Insulin resistance is rare
- Patients are insulin dependent
Signs and symptoms of DM type 1 and their respective pathogenesis

- Hyperglycemia
- Glycosuria
- Polyuria – osmotic diuresis
- Polydipsia – hyperosmolarity and dehydration
- Polyphagia – cellular fasting
- Weight loss – catabolism, negative E balance
- Fatigue – metabolic changes
- Poor wound healing – alterations in local
- Infections – and general immunity
LADA – characteristics
(Latent autoimmune diabetes in adults)

- Called Type 1.5 DM or slowly progressing insulin-dependent diabetes
- T cell mediated autoimmune disease
- Adult age at diagnosis (range 30-70 years)
- 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 1 DM’s predisposing genes (such as HLA-DR3, HLA-DR4, BW54, DQ-131-57-NON-ASP)
- Often accompanied by thyroid and gastric parietal cells organ specific antibodies
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

1. Primary disturbance:
   $\beta$ $\downarrow$ biological activity of insulin

2. Compensatory hyperinsulinemia
   $\beta$ due to $\uparrow$ concentration of blood glucose

3. Insulin resistance:
   $\beta$ $\downarrow$ ability of insulin to inhibit production of glucose in liver $\rightarrow$ $\uparrow$ glucose production
Mechanism of insulin action

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Insulin Resistance (IR)

Causes

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**
Natural History of Type II Diabetes

- Normal
- Impaired glucose tolerance
- Type 2 diabetes

- Insulin resistance
- Glucose level
- Insulin production

β-cell dysfunction
WHEN? ... not “If”

- Genetic predisposition
- Obesity
- Stress
- Insufficient/disturbed sleep
- Chemistry

1 kg weight = +5% risk

Obesity

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 - type2 development
Pathobiochemistry of DM (CH and Protein)

- Insulin
- Contrainsululary hormones
- Intake
- Digestion
- Absorption
- Glycogeno-lysis
- Glycolisis
- Glycogen
- Alanine
- Hyperglycemia
- Loss (if > 10 mmol.L⁻¹)
- Consumption
- Storage (E)
- Unsuppressed glucose production
- Insuline resistance
Do not forget the lipids!

TG

hsL

Glycerol + FFA

Ketones

C_{2n}  C_{2n-2}  C_{2n-4}  C_2

NAD  NADH  FAD  FADH

Stop
Signs and symptoms of DM type 2 ... and their absence

Mild polyuria
Mild polydipsia
Mild polyphagia
Genital itching

The symptoms of complications
Acute Complications

- Hypoglycemia and hypoglycemic coma
- Diabetic Ketone acidosis (DKA)
- Hyperosmolar diabetic coma (HDC)
Characteristics of ketoacidic and hyperosmolar coma

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ketoacidic coma</th>
<th>Hyperosmolar coma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type diabetes</td>
<td>Type 1</td>
<td>Type 2</td>
</tr>
<tr>
<td>Primary alteration</td>
<td>Excessive ketoacidosis</td>
<td>Excessive hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Ketones &gt;3 mmol/L; pH &lt;7.25</td>
<td>+ Osmolarity &gt; 330 mOsm/L</td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin + rehydration</td>
<td>Rehydration (hypovolemia!)</td>
</tr>
<tr>
<td>Age</td>
<td>Young</td>
<td>Elderly</td>
</tr>
<tr>
<td>Trigger</td>
<td>Infection, stress, trauma</td>
<td>Inadequate water intake</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor (50:50); 5% in DKA</td>
<td>Pessima</td>
</tr>
</tbody>
</table>
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
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
“Take no prisoners!”

- Stroke
- Diabetic eye disease (retinopathy, cataracts, glaucoma)
- Renal disease (glomerulopathies, pyelonephritis)
-Peripheral vascular disease
- Erectile Dysfunction (frequent urinary infections)
- Peripheral Neuropathy
- CAD and hypertension (2-4 X)
- Diabetic foot
Characteristics of two main types of diabetes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type I DM</th>
<th>Type II DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main pathogenetic link</td>
<td>Absolute insulin deficiency</td>
<td>Relative insulin deficiency</td>
</tr>
<tr>
<td>Heredity</td>
<td>50% cordance</td>
<td>100% cordance</td>
</tr>
<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 severe (fragile)</td>
<td>Light or asymptomatic</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>Acute complication</td>
<td>Ketoacidosis</td>
<td>Hyperosmolar coma</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>
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

1 in 3 people with diabetes do not know they have it

1 in 12 adults have diabetes
Diabetes - management

Early, long term, integrated, individualized

Diet control
Physical activity
Drug therapy
Education
Self-monitoring
HbA₁C – ultimate goal

Hb

Normoglycemia + Hyperglycemia

A1C

DIABETIC
> 6.5

PRE-DIABETIC
5.7 - 6.5

NORMAL
< 5.7

FPG

DIABETIC
> 7.0

PRE-DIABETIC
5.6 - 7.0

NORMAL
< 5.6

GTT

DIABETIC
> 11.1

PRE-DIABETIC
7.8 - 11.1

NORMAL
< 7.8
Indication for insulin therapy

1. Type I DM
2. Type II DM:
   - Acute complication: HDC, DKA
   - End stage of chronic complication
   - Stress
   - Pregnancy
   - Severe weight loss
   - Cortisol therapy
Thank you!