Metabolic changes in Diabetes mellitus (DM)

Dr. Howaida Nounou
College of science
Biochemistry department
• The abnormalities caused by absolute or relative insulin deficiency is called Diabetes Mellitus.

• It is characterized by abnormalities in the metabolism of carbohydrate, protein and fat, primarily due to deficiency in the synthesis, secretion or function of insulin.

• The disease is associated with microvascular, macrovascular, and metabolic complications.

• The hormone insulin is produced by the β cells in the islets of Langerhans situated in the pancreas.
• Normal fasting value of plasma glucose concentration: 
  < 6.1 mmol/l
• Normal value of postprandial glucose test (PGTT)– blood glucose concentration 2 hs after beginning of test < 7.8 mmol/l

• **New criteria for diagnosis of DM**

  1\textsuperscript{st}: classic symptoms and signs of DM are present (polyuria, polydipsia, weight loss), and increased day-time blood glucose concentration to 11.1 mmol/l and more
  or
  2\textsuperscript{nd}: fasting glucose level is 7.0 mmol/l and more
  or
  3\textsuperscript{rd}: 2 hours glucose level in PGTT is 11.1 mmol/l and more

  For confirmation of diagnosis DM positivity each of the mentioned parameters have to be confirmed next day by positivity any of the mentioned parameter

Dr. Howaida Nounou
Pancreas – functional anatomy of endocrine portion

- The adult pancreas is made up of collections of cells called islets of Langerhans.
There are four major cell types in the islets of Langerhans. They are,

- **α cells** - produce glucagon. Glucagon is catabolic, mobilizing glucose, fatty acids and amino acids from stores into the blood stream; tends to increase plasma glucose by stimulating hepatic glycogenolysis and gluconeogenesis; increases lipolysis in adipose tissue.

- **β cells** - produce insulin. Insulin is anabolic, increasing the storage of glucose, fatty acids and amino acids.

- **Δ cells** - produce somatostatin, which inhibits secretion of insulin, glucagon and pancreatic polypeptide.

- **F (or PP) cells** - responsible for the production of pancreatic polypeptide, which slows absorption of food.
Insulin – structure

Insulin is a polypeptide containing 2 chains of amino acids linked by disulfide bridges.
Effects of insulin

Rapid (seconds):
Increased transport of glucose, amino acids, and K+ into insulin sensitive cells.

Intermediate (minutes):
• Stimulation of protein synthesis
• Inhibition of protein degradation
• Activation of glycogen synthase and increased glycogenesis
• Inhibition of phosphorylase and gluconeogenic enzymes (decreased glycogenolysis and gluconeogenesis)

Delayed actions (hours):
• Increase in mRNAs for lipogenic and other enzymes (increased lipogenesis)
Insulin function

- Increased glucose uptake
- Increased glucose use and storage
- Increased protein synthesis
- Increased fat storage
On carbohydrate metabolism..

Reduces rate of release of glucose from the liver by
  • inhibiting glycogenolysis
  • stimulating glycogen synthesis
  • stimulating glucose uptake
  • stimulating glycolysis
  • inhibiting gluconeogenesis

Increases rate of uptake of glucose into all insulin sensitive tissues, notably muscle and adipose tissue.
Summary of Regulation of Glucose Levels

**Glucose**: major energy source

blood levels maintained by:

- **insulin**
- **glucagon**

\[ \text{glucose} \xrightarrow{\text{glycogenesis}} \Downarrow \text{glucose} \]

\[ \text{glucose} \xrightarrow{\text{glycogenolysis}} \Uparrow \text{glucose} \]
On lipid metabolism...

- Reduces rate of release of free fatty acids from adipose tissue.

- Stimulates de novo synthesis of fatty acids and also conversion of fatty acids to triglycerides in liver.
On protein metabolism...

• Stimulates transport of free amino acids across the plasma membrane in liver and muscle.

• Stimulates protein synthesis and reduces release of amino acids from muscle.
Actions......

• Insulin favors movement of potassium into cells Vigorous treatment with insulin (as in Diabetic ketoacidosis) will cause potassium to move into cells causing hypokalemia.

• Promotes general growth and development.
Glucose transporters

• Glucose enters cells by facilitated diffusion with the help of glucose transporters, GLUT 1 to GLUT 7.

• GLUT 4 is the glucose transporter in muscle and adipose tissue which is stimulated by insulin.

• Transport of glucose into the intestine and kidneys is by secondary active transport with sodium i.e. via SGLT 1 AND SGLT 2 (sodium dependent glucose transporters).
Major factors regulating insulin secretion

- Direct feedback effect of plasma glucose on β cells of pancreas.
- Tolbutamide and other sulfonylurea derivatives
- Stimuli that increase cAMP levels in β cells increase insulin secretion probably by increasing intracellular Ca 2+.
Mitochondria → TCA cycle → glucose → pyruvate

GLYCOLYSIS

PFK

insulin

Ca^{2+} 

ΔΨ

K^+

ATP

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Diabetes Mellitus

- Diabetes mellitus (DM) is a chronic disorder characterized by fasting hyperglycemia or plasma glucose levels that are above defined limits during oral glucose tolerance testing (OGTT).

**Type 1 Diabetes**
Immune mediated, absolute insulin deficiency due to autoimmune destruction of β cells in the pancreatic islets.

**Type 2 Diabetes**
Individuals with insulin resistance or insensitivity of tissues to insulin (later leading to impaired insulin secretion). Maybe due to deficiency of GLUT 4 in insulin sensitive tissues, or genetic defects in the insulin receptor or insulin molecule itself.
pathogenesis of DM

Type 1 DM - characteristics

- It is most typical in individuals under 30 years of age (juvenile DM)

80% - 90% of beta cells in the islets of Langerhans are destroyed

Possible mechanisms of beta cells destruction:

a) by islet cell antibodies of the IgG class

b) by non-immune mechanism (idiopathic up to now)
Evidence suggest that type 1 DM is caused by a gradual process of autoimmune destruction of beta cells in genetically susceptible individuals.

The result of beta cells destruction:

- almost no or absolute no functional insulin is produced
- glucagon is present in relative excess
- individuals are prone to ketoacidosis
- patients are insulin dependent
Who gets Type 2 Diabetes?

Most people are lead to believe that they’re to blame for the disease. However, this disease can also be inherited by genes as well. Not everyone that eats a lot of sugar and is overweight have the disease. But there are higher risks for people developing type 2 diabetes.
Here are some facts on how it is people obtain this disease:

- People who are overweight
- Have a parent or sibling with diabetes
- Are 40 years of age
- Had diabetes during pregnancy
- Have the stress of an illness or injury
- Had a baby that weighed more than 9 pounds at birth.
Secondary causes of diabetes

1. Other specific types (e.g., certain genetic defects; drug induced; etc)

2. Gestational diabetes mellitus (during pregnancy)
Diabetes is characterized by...

- Hyperglycemia
- Glycosuria
- Polydypsia
- Polyuria
- Polyphagia
- Ketosis, acidosis, coma
- eventually death if left untreated.
The fundamental defects are...

– Reduced entry of glucose into various peripheral tissues

– Increased liberation of glucose into circulation from liver. Therefore there is an extracellular glucose excess and in many cells an intracellular glucose deficiency – “starvation in the midst of plenty”.

– Various signs and symptoms in diabetes are due to disturbances in carbohydrate, protein and lipid metabolism.
Consequences of disturbed carbohydrate metabolism

- Polyuria, polydypsia and polyphagia are seen in some diabetic patients.

- The renal threshold for glucose is **180 mg%** i.e. if the plasma glucose value is raised above **180 mg%**, glucose will start appearing in urine (glycosuria). Thus, as glucose is lost in the urine, it takes along with it water (osmotic diuresis) leading to increased urination (polyuria). Since lot of water is lost in the urine, it leads to dehydration and increased thirst (polydypsia). Electrolytes are also lost in the urine.
Consequences of disturbed carbohydrate metabolism....

- The quantity of glucose lost in urine is enormous and thus to maintain energy balance the patient takes in large quantities of food.
Consequences of disturbed lipid metabolism

- The principal abnormalities are acceleration of lipid catabolism with increasing formation of ketone bodies and decreased synthesis of fatty acids and triglycerides.

- **Acidosis and ketosis** is due to overproduction of ketone bodies (acetoacetate, acetone and β-hydroxybutyrate).

- Most of the hydrogen ions liberated from acetoacetate and β-hydroxybutyrate are buffered, but still severe metabolic acidosis still develops.

- The low pH (metabolic acidosis) stimulates the respiratory center and produces the rapid, deep, regular breathing.
Consequences of disturbed lipid metabolism....

• The acidosis and dehydration can lead to coma and even death.

• Lipase converts triglycerides to free fatty acids (FFA) and glycerol. Insulin inhibits the hormone sensitive lipase in adipose tissue and in the absence of insulin, the plasma level of FFA doubles. In liver and other tissues, the FFA are catabolised to acetyl Co A, and the excess acetyl Co A is converted to ketone bodies.
Consequences of disturbed cholesterol metabolism

• In diabetics, the cholesterol level is usually elevated leading to atherosclerotic vascular disease.

• This is due to a rise in the plasma concentration of VLDL and LDL (which maybe due to increased production by the liver or decreased removal from circulation).
HbA1C

• The hemoglobin A1C percentage is a way of looking at average blood sugar control over a period of 3 months.

• When plasma glucose is episodically elevated over time, small amounts of hemoglobin A are nonenzymatically glycosylated to form HbA1C.

• Red blood cells live 90 to 120 days. This means that once sugar has combined with the hemoglobin in red blood cells, the hemoglobin A1C stays in the blood for 90 to 120 days. This means the amount of hemoglobin A1C in blood reflects how often and how high the blood sugar has been over the past 3 months.

• The hemoglobin A1C percentage rises as the average plasma glucose level rises.
Effects of insulin deficiency

• Carbohydrate Metabolism

• Protein Metabolism

• Lipid Metabolism
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<thead>
<tr>
<th>Metabolic defects</th>
<th>Chemical abnormalities</th>
<th>Clinical abnormalities</th>
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<tr>
<td><strong>Carbohydrate Metabolism</strong></td>
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<tr>
<td>1. Diminished uptake of glucose by tissues such as muscle, adipose tissue and liver</td>
<td>Hyperglycemia</td>
<td>Polyuria, polydipsia, polyphagia</td>
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<td>2. Overproduction of glucose (via glycogenolysis and gluconeogenesis) by the liver</td>
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<td>Blurred vision, Diminished mental alertness</td>
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<td>Fat Metabolism</td>
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<tr>
<td>1. Increased lipolysis</td>
<td>Elevated plasma fatty acids level</td>
<td>Loss of adipose tissue</td>
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<td></td>
<td>Elevated plasma glycerol level</td>
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<td>2. Decreased lipogenesis</td>
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<td>Loss of adipose tissue</td>
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<td>3. Decreased removal of</td>
<td>Elevated plasma and urine ketones</td>
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<td>ketones</td>
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<td>and increased ketone</td>
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If left untreated, Diabetes can cause many life threatening complications:

- **Blindness**
- **Chronic Renal Failure**= kidney failure
- **Atherosclerosis**= heart attacks and stroke
- **Diabetic Neuropathy**= numbness and pain to hands and feet
- **Foot Ulcers**
RISK FACTORS!

• Coma or death may occur as a result in Diabetic Ketoacidosis

• People who smoke are a much higher risk at heart attacks, stroke, infections, and problems with poor circulation
Thank you