Advanced Clinical Biochemistry

Disorder of Carbohydrates Metabolism

Grade 4-Fall 2020-2021
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Carbohydrate disorders

Introduction;

Human bodies rely on the oxidation of complex organic compounds to obtain energy.

Three general types of such compounds are;

  Carbohydrates, lipids, and proteins

What are carbohydrates?
Classification of carbohydrates

Monosaccharides eg, glucose, fructose, galactose

Disaccharides eg, sucrose, lactose, maltose

Polysaccharides eg, glycogen, starch, cellulose.
Digestion of dietary carbohydrates
GLUCOSE METABOLISM

• the cornerstone of life

• neurons are especially dependent on glucose

• regulatory mechanisms:
  – hyperglycemic hormones = glucagon
  – hypoglycemic hormone = insulin
Fate of glucose

Glycolysis

Gluconeogenesis

Glycogenolysis

Glycogenesis

Lipogenesis
Glycolysis

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Aerobic Glycolysis</th>
<th>Anaerobic Glycolysis</th>
<th>Pyruvate</th>
<th>Lactate</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyruvate dehydrogenase</td>
<td>NAD</td>
<td>NADH + H</td>
<td>CO2</td>
<td>TPP, CoA-SH, FAD, Lipoate</td>
</tr>
</tbody>
</table>

Acetyl CoA

<table>
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<tr>
<th>CO2</th>
<th>H2O</th>
<th>Energy</th>
<th>CO2 + H2O + Energy</th>
<th>Glucose</th>
<th>Aerobic Glycolysis</th>
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Clinical correlation (glycolysis)

Inhibition of pyruvate dehydrogenase (PDH) by alcohol

- Many alcoholics develop thiamine deficiency because alcohol inhibits the transport of thiamine through the intestinal mucosal cells, and consume thiamine in alcohol oxidation.
Thiamine is converted to thiamine pyrophosphate (TPP) and acts as a coenzyme of PDH.

Lack of TPP inhibits PDH enzyme as a result pyruvate is converted to lactate leading to lactic acidosis and neurological disorders.

Measurement of blood lactate is useful to assess the presence and severity of shock and to monitor the patients recovery.
Clinical correlation (glycolysis in cancer cell)

- It has been known that hypermetabolism of glucose occur in cancer cells. Cancer cell stimulate glucose uptake and glycolysis.

- As cancer cells grow more rapidly, blood vessels cannot supply efficiently to fulfill the required demand of O2 by rapidly grown tumour cells, begin to grow in hypoxic condition.
Regulation of carbohydrate metabolism

During a brief fast, glucose is supplied to the ECF from the liver through glycogenolysis. When the fasting period is longer than 1 day, glucose is synthesized from other sources through gluconeogenesis.

Control of blood glucose is under two major hormones: insulin and glucagon, both produce by the pancreas.
Postprandial hyperglycemia

- Insulin release
- Insulin-independent cells

- Liver storage: glycogen
- Glucose moves into insulin-dependent cells (muscle, adipose)
- Protein synthesis in liver
- Inhibition: lipolysis, glycogenolysis, gluconeogenesis
The action of hormones

Action of insulin

Increases glycogenesis

- Glucose $\rightarrow$ glycogen

Glucose $\rightarrow$ pyruvate $\rightarrow$ acetyl CoA

$CO_2 + H_2O+ \rightarrow$ Energy

Increases lipogenesis

Decreases glycogenolysis

Glycogen $\rightarrow$ glucose
Action of glucagon

Increases glycogenolysis

Glycogen → glucose

Increases gluconeogenesis
Physiological importance of carbohydrate metabolism:

The brain is highly dependent upon the extracellular glucose concentration for its energy supply; indeed, Hypoglycemia is likely to impair cerebral function or even lead to irreversible neuronal damage.

This is because the brain cannot;
• Synthesis glucose

• Store glucose in significant amount

• Metabolize substrates other than glucose and ketones (plasma ketone concentrations are usually very low and ketones energy are of little importance as an energy source under physiological conditions).

• Extract enough glucose from ECF at low concentrations for its metabolic needs, because entry into brain cells is not facilitated by insulin
Hyperglycemia

Hyperglycemia is an increase in plasma glucose levels, during hyperglycemia state, insulin is secreted by the beta cells of the pancreatic islets of Langerhans. Insulin enhances membrane permeability to cells in the liver, muscle, and adipose tissue.

Hyperglycemia, or increased plasma glucose levels, is caused by an imbalance of hormones.
Fasting hyperglycemia

- mobilization of substrates from muscle and adipose tissue
- accelerated hepatic gluconeogenesis, glycogenolysis, ketogenesis
- impaired removal of endogenous and exogenous fuels by insulin-responsive tissues.
Diabetes mellitus

Diabetes mellitus is actually a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.
### Classification of diabetes mellitus

<table>
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<tr>
<th>Classification</th>
<th>Pathogenesis</th>
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</table>
| Insulin dependent diabetes mellitus (IDDM) Type 1 | . beta- cell destruction  
. Absolute insulin deficiency  
. Autoantibodies  
. islet cell autoantibodies  
. insulin autoantibodies |
Non insulin dependent diabetes mellitus

(NIDDM) Type 2

• Insulin resistance with an insulin secretary defect

• Relative insulin deficiency
Gestational Diabetes

Glucose intolerance during pregnancy

Due to

• Metabolic,

• Hormonal changes.
Other

associated with secondary conditions

. genetic defects of beta cell function

. pancreatic disease

. endocrine disease

. insulin receptor abnormalities
Laboratory findings in hyperglycemia

• Increased glucose in plasma and urine
• Increased urine specific gravity
• Increased serum and urine osmolality
• Ketones in serum and urine (ketonemia and ketonurea)
• Decreased blood and urine pH (acidosis)
• Electrolyte imbalance
Criteria for the diagnosis of diabetes mellitus

1-Symptoms of diabetes mellitus plus random plasma glucose concentration $\geq 200$ mg/dL (11.1 mmol/L).

The classic symptoms of diabetes include;

polyurea, polydipsia, polyphagia, and unexplained weight loss.
OR

2- Fasting plasma glucose (FPG) ≥ 126mg/dL

(7.0 mmol/L)

OR

3- 2-Hour post load glucose ≥ 200 mg/dL   (11.1mmol/L), during an oral glucose tolerance test (OGTT), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
ADA diagnosis of DM

1. **classic symptoms** of diabetes (polyuria, polydipsia, and unexplained weight loss) *plus* random plasma glucose concentration $\geq 200$ mg/dL ($\geq 11.1$ mmol/L); or

2. **fasting** ($\geq 8$-hour) plasma glucose concentration $\geq 126$ mg/dL ($\geq 7.0$ mmol/L); or

3. a **2-hour postload** plasma glucose concentration $\geq 200$ mg/dL ($\geq 11.1$ mmol/L) during a 75-g oral glucose tolerance test.
Late complications of diabetes mellitus

• Microangiopathy is characterized by abnormalities in the walls of small blood vessels.
  - Retinopathy
  - Nephropathy - renal failure
  - Neuropathy – may become evident as diarrhea, postural hypotension, impotence, neurogenic bladder and neuropathic foot ulcers.

• Macroangiopathy (or accelerated atherosclerosis) leads to premature coronary heart disease.
Glycosylated hemoglobin/ hemoglobin A1c

Glycosylated hemoglobin is the term used to describe the formation of a hemoglobin compound produced when glucose (a reducing sugar) reacts with the amino group of hemoglobin (a protein).

The glucose molecule attaches nonenzymatically to the hemoglobin molecule to form a ketamine. The rate of formation is directly proportional to the plasma glucose concentrations.

Because the average red blood cell lives approximately 120 days, the glycosylated hemoglobin level at any one time reflects the average blood glucose level over the previous 2-3 months.
Hemoglobin A1c (HbA1c), the most commonly detected glycosylated hemoglobin, is a glucose molecule attached to one or both N-terminal valines of the beta polypeptide chains of normal adult hemoglobin.

Normal values range from 4.5-6 mmol/L.
The specimen requirement for HbA1c measurement is an EDTA whole blood sample. Before analysis, a hemolysate must be prepared. The methods of measurement are grouped into two major categories;

1- Based on charge differences between glycosylated and nonglycosylated hemoglobin (cation-exchange chromatography, electrophoresis, and isoelectric focusing).

2- Structural characteristics of glycogroups on hemoglobin (affinity chromatography and immunoassay).