Blood Glucose Disorders

**Objectives:**
1. Understand the importance of glucose as a major energy source.
2. Describe the hormonal regulation of blood glucose.
3. Define the terms hypoglycemia and hyperglycemia.

**Blood Glucose**

Glucose is the most important carbohydrates available to the body for production of energy. Brain tissue and RBCs mainly depend on glucose for their energy requirement.

**Sources:**
1. Exogenous: diet.
   b. Gluconeogenesis.

Glucose is essential to the brain since the brain:
1. Can't synthesize glucose.
2. Can't store glucose.
3. Can't utilize substrate other than glucose and ketones.

Renal tubular cells reabsorb almost all the glucose filtered by the glumeruli and urinary glucose concentration is normally too low to be detected by the usual tests, even after a carbohydrate meal.

**Hormonal control:**
1. **Insulin:** peptide hormone produced by β-cells of Islets of Langerhans of the pancreas. It is an anabolic hormone, its actions are:
   a. Stimulates the uptake of glucose into tissues.
   b. Promote the conversion of glucose to glycogen or fat for storage.
   c. Inhibits gluconeogenesis & glycogenolysis.
   d. Stimulates protein synthesis & inhibits protein breakdown.
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2. **Glucagon**: polypeptide hormone secreted by α-cells of the pancreas; its actions are:
   a. Stimulate the production of glucose in the liver by glycogenolysis and gluconeogenesis.
   b. Inhibits glycolysis.
   c. Depresses glycogen synthesis.

   - Insulin antagonizes the effect of glucagon and also inhibits the glucagon release from the pancreas.

3. **Adrenaline**: a catecholamine secreted by adrenal medulla; its actions are:
   a. Stimulates glycogenolysis & decrease glucose utilization.
   b. Stimulates glucagon secretion & inhibits insulin secretion by the pancreas.

4. **Growth hormone**: a polypeptide secreted by the anterior pituitary:
   a. Stimulates gluconeogenesis and lipolysis.
   b. Antagonizes insulin stimulated glucose uptake.

5. **Cortisol**: is secreted by the adrenal cortex:
   a. Stimulates gluconeogenesis.
   b. Increase breakdown of protein & fat.

HYPOGLYCEMIA

It is defined as plasma glucose concentration <2.5 mmol/L in a tube containing an inhibitor of glycolysis.

**Symptoms**: sweating, tachycardia, and agitation; may develop into faintness, dizziness, lethargy and finally coma that can cause permanent cerebral damage.

**Investigations:**

1. Plasma glucose.
2. Insulin level.
3. Imaging; CT scan.
Disorders of Glucose Metabolism

Causes:

<table>
<thead>
<tr>
<th></th>
<th>With ↑ insulin</th>
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<tbody>
<tr>
<td>1</td>
<td>1. Insulinoma: a small benign tumor.</td>
<td>2. Exogenous insulin: overtreatment of DM.</td>
</tr>
<tr>
<td>2</td>
<td>With ↓ insulin</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Neonatal hypoglycemia</td>
<td>In premature infants; caused by:</td>
</tr>
<tr>
<td>4</td>
<td>Pseudohypoglycemia</td>
<td>In vitro glucose metabolism caused by:</td>
</tr>
</tbody>
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<table>
<thead>
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<tbody>
<tr>
<td>1</td>
<td>Adrenal or pituitary insufficiency.</td>
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<tr>
<td>2</td>
<td>Inherited metabolic disorders: glycogen storage disease type I.</td>
</tr>
<tr>
<td>1</td>
<td>Low glycogen stores.</td>
</tr>
<tr>
<td>2</td>
<td>Poor feeding.</td>
</tr>
<tr>
<td>1</td>
<td>Old blood sample.</td>
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<tr>
<td>2</td>
<td>Not collected with NaF anticoagulant.</td>
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</table>

Treatment:

1. Mild hypoglycemia: oral glucose.
2. Severe hypoglycemia: IV glucose.
3. Good control of DM.
4. Surgery to remove tumors.

Hyperglycemia:

1. IV infusion.
2. Severe stress has a transient effect as in trauma, MI and CVA.
Objectives:

1. Define diabetes and discuss its metabolic risk to patients.
2. Identify the main types of DM; (type1, type2 & GDM).
3. Enumerate the major short term & long term complications of DM.

Definition:

DM is a group of syndromes characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.

Classification:

The American diabetes association/World Health Organization Guidelines recommend the following categories of diabetes:

1. Type 1 DM.
2. Type 2 DM.
3. Gestational DM (GDM): it is any degree of glucose intolerance with onset or first recognition during pregnancy due to metabolic and hormonal changes; it is associated with:
   a) ↑ Risk for fetal abnormalities.
   b) ↑ Perinatal complications.
   c) ↑ Risk of developing DM in later years.

Signs and symptoms:

Polydipsia, polyuria,& polyphagia. In addition; Type 2 DM is associated with obesity, smoking, dyslipidemia and hypertension; while type 1 DM is associated with rapid weight loss, mental confusion and possible loss of consciousness.
The following table shows a comparison of type 1 and type 2 diabetes:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Type 1 diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Age of onset</td>
<td>Usually during Childhood; symptoms develop rapidly</td>
<td>Frequently after age 35; symptoms develop gradually</td>
</tr>
<tr>
<td>2 Nutritional status at time of disease onset</td>
<td>Frequently undernourished</td>
<td>Obesity usually present</td>
</tr>
<tr>
<td>3 Prevalence</td>
<td>10% of diagnosed diabetics</td>
<td>90% of diagnosed diabetics</td>
</tr>
<tr>
<td>4 Genetic predisposition</td>
<td>Moderate</td>
<td>Very strong</td>
</tr>
<tr>
<td>5 Autoimmunity or anti-insulin antibody</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>6 Defect or deficiency</td>
<td>β cells are destroyed, eliminating production of insulin</td>
<td>Insulin resistance combined with inability of β cells to produce the appropriate quantities of insulin</td>
</tr>
<tr>
<td>7 Frequency of ketosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>8 Plasma insulin level</td>
<td>Low or absent</td>
<td>High early in disease; low in disease of long duration</td>
</tr>
<tr>
<td>9 Acute complications</td>
<td>Diabetic ketoacidosis (DKA)</td>
<td>Hyperosmolar coma</td>
</tr>
<tr>
<td>10 Response to oral drugs</td>
<td>Unresponsive</td>
<td>Responsive</td>
</tr>
<tr>
<td>11 Treatment</td>
<td>Insulin is always necessary for life-long treatment</td>
<td>Diet, exercise, oral drugs; insulin may or may not be necessary.</td>
</tr>
</tbody>
</table>
Disorders of Glucose Metabolism

Acute Metabolic (Short-Term) Complications of DM:

A) HYPOGLYCEMIA: may be due to overtreatment with insulin or missing a meal, it is very common and may occur in 90% of type 1 diabetic patients and require prompt management which is immediate administration of glucose.

B) DIABETIC KETOACIDOSIS (DKA): this may be the presentation in 25-40% of type 1 DM, it is characterized by the following biochemical findings:

- Hyperglycemia.
- Ketosis.
- Acidosis.
- Glycosuria and ketonuria.
- Electrolyte disturbance and dehydration.
- Increased amylase enzyme.
- Increased VLDL and hypertriglyceridemia.

Management:

- Rehydration.
- Insulin IV infusion.
- Continuous monitoring of fluid and electrolytes.

C) HYPEROSMOLAR NON-KETOTIC COMA (HONK):

The individual with type 1 diabetes has higher tendency to produce ketones. Patients with type 2 DM seldom generates ketones, but instead have a greater tendency to develop hyperosmolar state. The difference in glucagon and insulin concentrations in these two groups appears to be responsible for the generation of ketones through β-oxidation.

In type 1, there is an absence of insulin with an excess of glucagon. This permits gluconeogenesis and lipolysis to occur. In type 2, insulin is present in as is (at times) hyperinsulinemia; therefore, glucagon is attenuated and fatty acid oxidation is inhibited. This will cause fatty acids to incorporate into triglycerides for release of VLDL.
Disorders of Glucose Metabolism

Long Term Complications of DM:

- Angiopathy
- Neuropathy
- Nephropathy
- Vascular
  - Proteinuria
- Skin Ulcers
  - ↑ susceptibility to Infections

Macrosvascular

- CAD
- CVA

Microvascular

- Retinopathy
Objectives:

1. Describe the role of Laboratory Investigations in the diagnosis of diabetes mellitus.
2. Understand the importance of monitoring Glycemic control and assessing complications in Diabetic patients.
3. Enumerate the major Indications of measuring blood glucose.
4. Define Metabolic syndrome & list its diagnostic criteria.

Introduction:

The treatment of DM is aimed at relieving symptoms and preventing both short & long term complications. The efficacy of treatment, whether with insulin, oral glucose lowering agents or dietary modifications alone, can be assessed clinically & by several biochemical laboratory investigations.

The Role of Laboratory Investigations includes:

1. **Diagnosis of DM:**
   The diagnostic criteria for DM are shown in the following table:

   1. Random plasma glucose $\geq 200$ mg/dl (11.1 mmol/L) + symptoms of DM
   2. Fasting plasma glucose $\geq 126$ mg/dl (7.0 mmol/L)
   3. Two-hour plasma glucose $\geq 200$ mg/dl (11.1 mmol/L) during an OGTT

   *In the absence of symptoms; the test should be confirmed on a subsequent day before confirming the diagnosis of DM.*
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2. Monitoring of glycemic Control:

The ADA has recommended that individuals with DM should monitor their glucose level regularly in an effort to maintain the blood glucose concentrations within or near the nondiabetic range with a minimal number of fluctuations. This can be achieved by the following tests:

- Self Monitoring (point of care testing-glucometer).
- Conventional laboratory glucose measurement.

A. Short term:

B. Long term: by measuring Glycated Hemoglobin (HbA1c):

This is a term used to describe the formation of a hemoglobin compound formed when glucose reacts with the amino group of hemoglobin nonenzymatically.

It is expressed as a percentage of the total blood hemoglobin concentration; the higher the percentage, the poorer is glycemic control. Normal level of HbA1c should be ≤ 5.4%; however, the recommended level for acceptable glycemic control in DM is ≤ 7%.

The rate of formation is directly proportional to the plasma glucose concentration. Because the average RBC lives approximately 120 days, HbA1c level at anytime reflects the average blood glucose level over the previous 2-3 months. HbA1c is a reliable method for monitoring long-term DM control rather than RBS or FBS.

3. Assessment of DM Complications:

1) Blood glucose measurement for diagnosis of Hypoglycemia.
2) Ketones are assessed in plasma or urine in DKA.
3) Microalbuminuria is the first and most important indicator of Diabetic Nephropathy.
4) Lipid Profile to assess the risk for angiopathy.

4. Diagnosis of the cause of glucose metabolic disorder:

1) Measuring Insulin in hypoglycemia.
2) Detecting Autoantibodies in Type 1 DM.
3) Assessing Pancreatic function.
4) Estimation of Hormones of the Counter-Regulatory mechanism.
Indications for Measuring blood Glucose:

1. All adults > 45 years.
2. Strong family history of DM.
3. History of GDM and/or bad obstetrical history.
4. Presence of Impaired fasting glucose (IFG).
5. Presence of Impaired Glucose Tolerance (IGT).
6. Obesity especially central adiposity.
7. Hypertension > 140/80 mmHg.
8. Decreased HDL < 35 mg/dl.
9. Increased TG > 250 mg/dl.
10. Sedentary life style and lack of exercise.

Obesity & Glucose Intolerance:

Obesity is the most common cause of insulin resistance; however, insulin resistance alone will not lead to type 2 DM in the absence of β-cell dysfunction. Pre-diabetic obese individuals can compensate for insulin resistance with elevated level of insulin; that is why insulin secretion is two to three times higher in obese subjects than it is in lean individuals.

Insulin resistance increases with weight gain and, conversely, diminishes with weight loss. This suggests that fat accumulation is important in the development of insulin resistance. Adipose tissue is not simply an energy storage organ, but also a secretary organ. Regulatory substances produced by adipocytes include leptin, and adiponectin may contribute to the development of insulin resistance.

Metabolic Syndrome:

It is a combination of medical disorders that, when occur together, increase the risk of developing cardiovascular disease and DM. Often a person with abnormal glucose tolerance will be found to have at least one or more of the other cardiovascular disease risk factors such as hypertension, central (upper body) obesity, and dyslipidaemia. This clustering has been labeled diversely as the metabolic syndrome, syndrome X, the insulin resistance syndrome, or Reaven's syndrome (named after Gerald Reaven).

Diagnosis:

Presence of any THREE of the following FIVE criteria:
## Disorders of Glucose Metabolism

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Defining level</th>
</tr>
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<tbody>
<tr>
<td>1 Abdominal obesity</td>
<td>Men: Waist circumference &gt;102 cm (&gt;40 inches)</td>
</tr>
<tr>
<td></td>
<td>Women: Waist circumference &gt;88 cm (&gt;35 inches)</td>
</tr>
<tr>
<td>2 High levels of triglycerides</td>
<td>&gt; 150 mg/dL</td>
</tr>
<tr>
<td>3 Low HDL cholesterol</td>
<td>Men: &lt;40 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Women: &lt;50 mg/dL</td>
</tr>
<tr>
<td>4 High blood pressure</td>
<td>&gt; 130/85 mmHg</td>
</tr>
<tr>
<td>5 High fasting glucose</td>
<td>≥ 110 mg/dL</td>
</tr>
</tbody>
</table>

Alone, each component of the cluster conveys increased cardiovascular disease risk, but as a combination they become much more powerful. This means that the management of persons with hyperglycaemia and other features of the metabolic syndrome should focus not only on blood glucose control but also include strategies to reduce the impact of other cardiovascular disease risk factors.

The metabolic syndrome with normal glucose tolerance identifies the subject as a member of a group at very high risk of future diabetes. Thus, vigorous early management of the syndrome may have a significant impact on the prevention of both diabetes and cardiovascular disease, especially as it is well documented that the features of the metabolic syndrome can be present for up to 10 years before glycaemic disorder is detected.

### References: