Lect .2

Clinical Chemistry

Carbohydrate Metabolism & Related Disorders

Ketosis

During fasting, when exogenous glucose is unavailable and the plasma insulin concentration is therefore low,

Endogenous TG are reconverted to free non-esterified fatty acids (NEFAs) and glycerol by lipolysis .

Both are transported to the liver cells , in plasma the NEFA being protein bound, predominantly to albumin.

Glycerol enters the hepatic gluconeogenic pathway at the triose phosphate stage; then the synthesized glucose can be released into circulation , thus minimizing the fall in glucose concentrations .

Ketosis occurs when fat stores are the main energy source and may result from fasting or from reduced nutrient absorption, for example due to vomiting.

Mild ketosis may occur after as little as 12 h of fasting.

After short fast metabolic acidosis is not usually detectable,

But after longer periods, more hydrogen ions may be produced than can be dealt with by homeostatic buffering mechanisms, depleting the plasma bicarbonate conc. , which therefore falls .

The plasma glucose concentration is maintained principally by hepatic gluconeogenesis, but during prolonged starvation, such as that in anorexia nervosa or during childhood, ketotic hypoglycaemia may occur.

Lactic Acidosis

Lactic acid, produced by anaerobic glycolysis, may either be oxidized to CO2 and water in the TCA cycle or be reconverted to glucose by gluconeogenesis in the liver.

***Both the TCA cycle and gluconeogenesis need oxygen; anaerobic glycolysis is a non-oxygen-requiring pathway.**

Pathological accumulation of lactate may occur because:

1-Production Is Increased By An Increased rate of Anaerobic Glycolysis,

2- Its Utilization Is Decreased By Impairment of The TCA Cycle or Impairment of Gluconeogenesis.

Tissue hypoxia due to the **poor tissue perfusion** of the '**shock**' **syndrome** is usually the **most common cause of lactic acidosis**.

Hypoxia increases plasma lactate conc. because:

- the **TCA cycle** cannot function anaerobically and **oxidation of pyruvate and lactate** to CO2 and water is thus **impaired,**

- Hepatic and renal gluconeogenesis from lactate cannot occur anaerobically,
- Anaerobic glycolysis is stimulated because the falling adenosine triphosphate (ATP) levels cannot be regenerated by the TCA cycle under anaerobic conditions.

Severe hypoxia can occur :

- following a **cardiac arrest**, causes marked lactic acidosis

- If **diabetic ketoacidosis DKA** is associated with significant volume depletion, this hypoxic syndrome may aggravate the acidosis.

GLUCOSE TRANSPORTERS

The transport of glucose into cells is modulated by two families of proteins.

- **1-The sodium-dependent glucose Transporters (SGLTs) use the electrochemical sodium gradient to transport glucose against its conc. gradient.**

- **SGLTs promote the uptake of glucose and galactose from the lumen of the small bowel and their reabsorption from urine in the kidney.**

- **2- Members of the second family of glucose carriers are called *facilitative glucose transporters* GLUT**

These transporters are designated GLUT-1 to GLUT -14, based on the order in which they were identified.

TABLE 46-1 Facilitative Human Glucose Transporters

Name	Class	Tissue	Function
GLUT1	I	Wide distribution, especially brain, kidney, colon, and fetal tissues	Basal glucose transport
GLUT2	I	Liver, β-cells of pancreas, small intestine, and kidney	Non–rate-limiting glucose transport
GLUT3	I	Wide distribution, especially neurons, placenta, and testis	Glucose transport in neurons
GLUT4	I	Skeletal muscle, cardiac muscle, adipose tissue	Insulin-stimulated glucose transport

GLUT5	II	Small intestine, kidney, skeletal muscle, brain, and adipose tissue	Transports fructose (not glucose)
GLUT6	III	Brain, spleen, leukocytes	
GLUT7	II	Intestine, testis, prostate	
GLUT8	III	Testis, heart, brain	
GLUT9	II	Kidney, liver	
GLUT10	III	Liver, pancreas	
GLUT11	II	Pancreas, kidney, placenta, skeletal muscle	
GLUT12	III	Heart, prostate	
HMIT		Brain	Transports *myo*-inositol (not glucose)
GLUT14	III	Testis	

They can be divided into three classes, based on sequence similarities and characteristics.

The best characterized are class I. Less is known about those in classes II and III.

- GLUT1 is widely expressed and provides many cells with their basal glucose requirement.

- GLUT1 in BBB and GLUT3 in neuronal cells provide the constant high concentrations of glucose required by the brain.
- GLUT2 is expressed in hepatocytes, β-cells of the pancreas, and basolateral membranes of intestinal and renal epithelial cells. It is a low-affinity, high-capacity transport system that allows non–rate-limiting movement of glucose into and out of these cells.

- **GLUT4 catalyzes the rate limiting step for glucose uptake and metabolism in skeletal muscle, the major organ of glucose consumption.**

- **GLUT4 is also present in adipose tissue.**

When circulating insulin concentrations are low, most of the GLUT4 is localized in intracellular compartments and is inactive.

After eating, the pancreas releases insulin, which stimulates the translocation of GLUT4 to the plasma membrane, thereby promoting glucose uptake into skeletal muscle and adipose tissue.

Insulin-stimulated glucose transport into skeletal muscle is defective in type 2 diabetes mellitus, but the mechanism has not yet been established.

Insulin-like growth factors 1 and 2 (IGF-1 and IGF-2)

are polypeptides structurally related to insulin.

***These hormones (previously referred to as *non-suppressible insulin-like activity* or *somatomedin*) exhibit metabolic and growth promoting effects similar to those of insulin.**

* **Accumulating evidence implicates the IGF axis in the development of several common cancers.**

IGF-1 (previously known as somatomedin C) is an important mediator of growth hormone action and is one of the major regulators of cell growth and differentiation.

The physiologic role of IGF-2 is not fully known yet.

Synthesis of IGF-1 depends on growth hormone and occurs predominantly in the liver.

In addition, many other cells produce IGF-1 that does not enter the circulation but acts locally.

Circulating IGF concentrations are approximately 1000-fold higher than insulin concentrations,

The hormone is kept inactive by binding to a family of at least six specific binding proteins.

These proteins regulate IGF by protecting the ligands in the circulation and delivering them to their target tissue.

*In contrast to insulin, which is unbound in the circulation,

less than 10% of total serum IGF-1 is free.

The biological actions of IGF are exerted through specific

IGF receptors or the insulin receptor.

The IGF-1 receptor is closely related to insulin receptor in structure and biochemical properties.

While, the IGF-2 receptor is quite different; it lacks tyrosine kinase activity, and its physiologic relevance is not understood.

- IGF-1 receptor has a high affinity for both IGF-1 and IGF-2, but a low affinity for insulin.

- IGF-2 receptor has high, low, and no affinity for IGF-2, IGF-1, and insulin, respectively.

- Insulin receptor binds insulin with high affinity and IGF-1 and IGF-2 with low affinity .

HYPERGLYCAEMIA & DIABETES MELLITUS

Hyperglycaemia may be due to:

- Severe stress (usually a transient effect) such as trauma, myocardial infarction(MI) or cerebrovascular Accidents (CVA),
- Diabetes mellitus(DM) or impaired glucose regulation .

Diabetes mellitus DM

Diabetes mellitus is caused by an absolute or relative insulin deficiency.

It has been defined by the World Health Organization (WHO),

on the basis of laboratory findings:

Criteria for Diagnosis of DM

➢FPG ≥ 126 mg/dL (7.0 mmol/L) on more than one occasion or once in the presence of symptoms (polytrid). Fasting is defined as no caloric intake for at least 8 h

OR

➢2h PG≥ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

- **A1C ≥ 6.5% (48 mmol/mol).**

- **OR**

- **In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, & a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).**

Classification of DM

1. **Type 1 diabetes (due to autoimmune β -cell destruction, usually leading to absolute insulin deficiency)**

2. **Type 2 diabetes (due to a progressive loss of adequate β-cell insulin secretion frequently on the background of insulin resistance)**

3. Gestational diabetes mellitus GDM

(diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)

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4. Specific Types of Diabetes due to other causes;-

e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, or after organ transplantation) , latent autoimmune diabetes in adults (LADA)