# Lab: 2

## “Glucose metabolism and diabetes mellitus”

### Glucose homeostasis:

The liver plays a key role in maintaining blood (glucose). After a carbohydrate-containing meal, it removes about 70% of the glucose load that is delivered via the portal circulation. Some of the glucose is oxidized and some is converted to glycogen for use as a fuel under fasting conditions. Glucose in excess of these requirements is partly converted by the liver to fatty acids and triglycerides, which are then incorporated into very low density lipoproteins (VLDLs) and transported to adipose tissue stores.

In the fasting state, blood (glucose) is maintained by glycogen breakdown in the liver in the short term, while glycogen stores last, and then by gluconeogenesis (from glycerol, lactate and pyruvate and from the gluconeogenic amino acids), occurring mostly in the liver, but also in the kidneys. Glucose is spared, under fasting conditions, by the ability of muscle and other tissues to adapt to the oxidation of fatty acids, and by the ability of the brain and some other organs to utilize ketone bodies that are formed under these conditions.

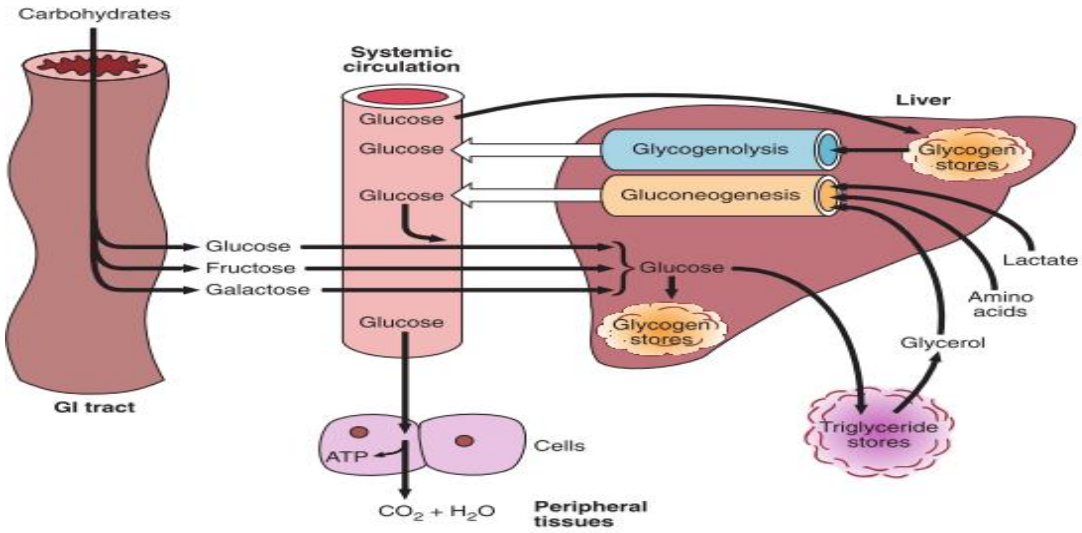


Figure (1): Glucose homeostasis

## Hormones concerned with glucose homeostasis:

The hormones mainly concerned with regulating glucose metabolism in the fed and fasting states are insulin, glucagon, growth hormone, adrenalin and cortisol. Insulin is the only hormone that lowers blood glucose. Glucagon, growth hormone, adrenalin and cortisol all tend, to antagonize the actions of insulin.

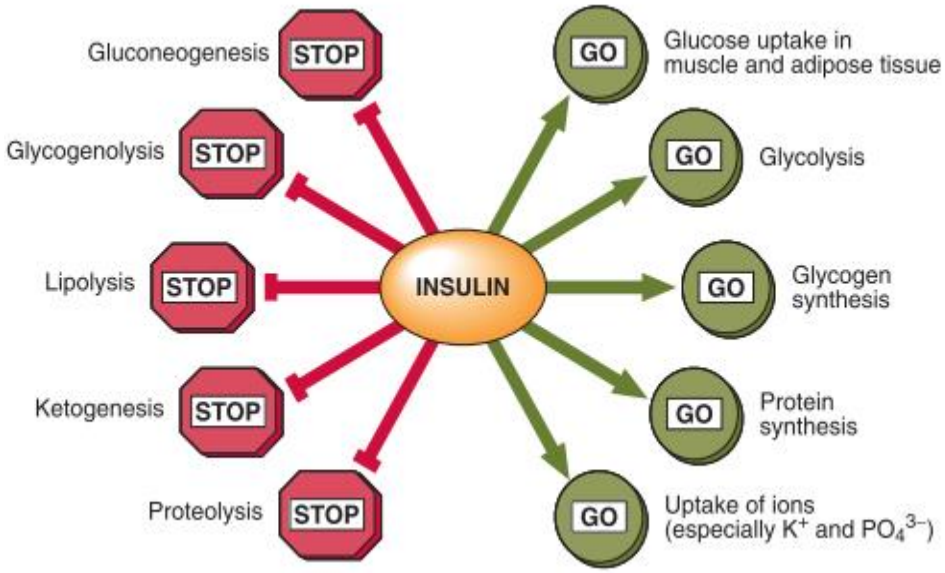


Figure (2): The actions of insulin

## Diabetes Mellitus:

Diabetes mellitus is a chronic metabolic disease characterized by elevated plasma glucose levels as a consequence of insulin deficiency, impaired action of insulin secondary to insulin resistance, or a combination of both abnormalities.

Diabetes mellitus can be classified into: Type 1 diabetes mellitus and type 2 diabetes mellitus. Other specific types of diabetes mellitus (secondary diabetes mellitus may result from pancreatic disease, endocrine disease such as Cushing's syndrome, drug therapy, and rarely, insulin receptor abnormalities).

## Diagnosis and Monitoring of DM:

The decision of diagnosis of D.M depends firstly on whether the patient is symptomatic or not. In symptomatic patient (polyuria, polydipsia, polyphagia, and weight loss) a single reading of

a- Fasting venous plasma glucose concentration of 7.0 mmol/L (126 mg/dl) or more or

b- a random venous plasma glucose concentration of 11.1 mmol/L (200 mg/dl) or more or

c- $HbA_{1c}$ of equal to or more than 6.5%

Is sufficient for diagnosis

In asymptomatic patient 2 repeated readings of

a- Fasting venous plasma glucose concentration of 7.0 mmol/L (126 mg/dl) or more or

b- $HbA_{1c}$ of equal to or more than 6.5%

Are needed to make the diagnosis.

Note: The same test should be used when repeating the measurement for confirmation. Sometimes an oral glucose tolerance test (OGTT) may be required to establish the diagnosis in equivocal cases.

An OGTT is usually performed after an overnight fast (for at least 10 hr. but not more than 16 hr.). A standard dose of 75 g of anhydrous glucose in 300 ml of water is given by mouth over a 5 minutes period. Blood specimens are collected before giving the glucose load and after 2 hr. As shown in table (1).

| **Venous plasma** | **Fasting** | **2 h post-75 g glucose** |
|---|---|---|
| Normal individuals | **<6.1** | **<7.8** |
| Diabetes mellitus | **≥7.0** | **or ≥11.1** |
| impaired glucose tolerance (IGT) | **<7.0 and** | **≥7.8 and <11.1** |
| Impaired fasting glucose (IFG) | **≥6.1 and <7.0** | **<7.8** |

Table 1: Interpretation of the oral glucose tolerance test (glucose mmol/L)

## Gestational diabetes mellitus:

The detection and treatment of GDM may reduce the risk for several adverse prenatal outcomes (such as excessive fetal growth and birth trauma, fetal death or neonatal morbidity).Women at high risk for GDM include those who have had GDM before, have previously given birth to a high-birth weight baby, are obese, have a family history of diabetes mellitus and/or are from high-risk ethnic groups, for example black or South Asian. These women should be screened at the earliest opportunity and, if normal, retested at about 24–28 weeks, as glucose tolerance progressively deteriorates throughout pregnancy. In some units 50 g oral glucose is used and the blood glucose is sampled at 1 h – plasma glucose of more than or equal to 7.8 mmol/L being diagnostic (O'Sullivan's screening test for gestational diabetes). If fasting venous plasma glucose is 7.0 mmol/L or more and/or the random measurement gives a concentration of 11.1 mmol/L or more (some doctors prefer to use a lower cut-off of about 9.0 mmol/L in pregnancy), the woman has GDM. In equivocal cases, an OGTT is indicated. Six weeks post-partum, the woman should be reclassified with a repeat OGTT.

## Glycated haemoglobin:

Glycated haemoglobin (HbA1c) is formed by non-enzymatic glycation of haemoglobin and is dependent on the mean plasma glucose concentrations and on the lifespan of the red cell; falsely low values may be found in patients with haemolytic disease.

This was expressed as a percentage of total blood haemoglobin concentration and gives a retrospective assessment of the mean plasma glucose concentration during the preceding (6–8 weeks). The higher the glycated haemoglobin, the poorer the mean diabetic or glycaemic control. Normal value <5.7%, however values that are equal to or more than 6.5% regarded as diabetes.

## Fructosamine:

The measurement of plasma fructosamine concentrations may be used to assess glucose control over a shorter time course than that of $HbA_{1c}$ (about 2–4

weeks), but the assay has methodological limitations. Fructosamine reflects glucose bound plasma proteins, predominantly albumin, which has a plasma half-life of about 20 days but is problematic in patients with hypoalbuminaemia. This assay may sometimes be useful in pregnancy and haemolytic disease (in whom $HbA_{1c}$ is difficult to measure and interpret).

## Glycosuria:

Glycosuria typically occurs when the plasma glucose concentration is greater than 180 mg/dl (10.0 mmol/L) (renal threshold).

Glycosuria may be due to:

- diabetes mellitus,
- glucose-containing infusion,
- renal glycosuria, which may be inherited as an autosomal dominant trait or in Fanconi's syndrome,
- pregnancy.

So the presence or absence of glycosuria has no role in the screening or the diagnosis of DM.

## Ketones in urine or blood:

The term 'ketone bodies' refers to acetone and the keto-acids acetoacetate and β-hydroxybutyrate. These are frequently found in uncontrolled diabetes (diabetic ketoacidosis). They are also found in normal subjects as a result of starvation or fasting, and sometimes in alcoholic patients with poor dietary intake (alcoholic ketoacidosis).

## Complications of DM:

Late complications of DM:

■ Retinopathy ■ Nephropathy ■ Neuropathy

■ Macroangiopathy and Microangiopathy

## Acute metabolic complications of DM:

### Diabetic Ketoacidosis (DKA):

Is a medical emergency usually occur in type I D.M. All metabolic disturbances seen in DKA are the indirect or direct consequences of the lack of insulin (as shown in figure 3).

Decreased glucose transport into tissues leads to hyperglycemia, which gives rise to glycosuria. Increased lipolysis causes overproduction of fatty acids, some of which are converted into ketones, giving ketonaemia, metabolic acidosis and ketonuria. Glycosuria causes an osmotic diuresis, which leads to the loss of water and electrolytes – sodium, potassium, calcium and other inorganic constituents.

Dehydration, if severe, produces prerenal uraemia and may lead to hypovolaemic shock. The severe metabolic acidosis is partially compensated by an increased ventilation rate (Kussmaul breathing). Frequent vomiting is usually present and exacerbate the loss of water and electrolytes. Plasma glucose concentrations are usually in the range 20–40 mmol/L.

The most common precipitating factors in the development of DKA are (infection, myocardial infarction, trauma or omission of insulin).

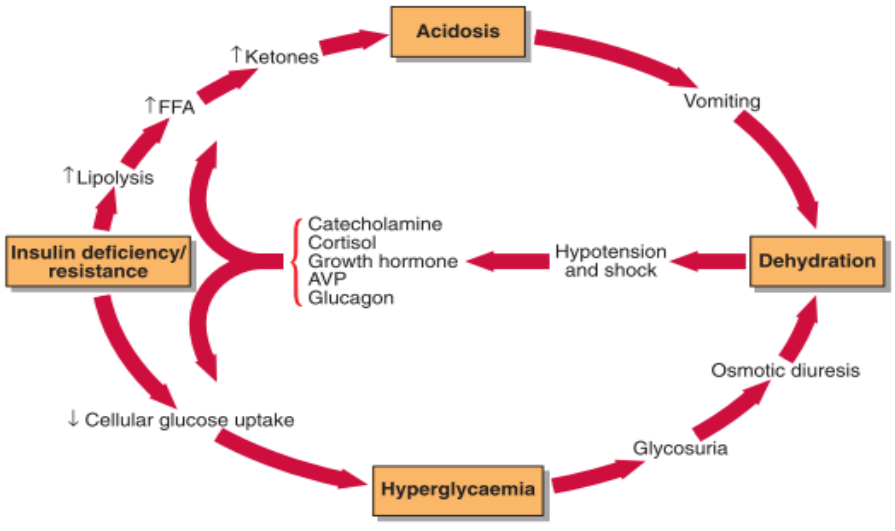


Figure (3): The development of diabetic ketoacidosis

## Hyperosmolar non-ketotic coma (HONK):

It usually occur in elderly, Type 2 diabetics, and develops relatively slowly over days or weeks. Insulin deficiency has the same effect on carbohydrate metabolism in DKA, but in HONK the level of insulin is sufficient to prevent ketosis but does not prevent hyperglycaemia and osmotic diuresis. Precipitating factors include severe illness, dehydration, glucocorticoids, diuretics, parenteral nutrition, dialysis and surgery. Extremely high blood glucose levels (above 50 mmol/L) accompany severe dehydration resulting in impaired consciousness.

## Hypoglycaemia:

This is probably the most common cause of coma seen in diabetic patients. Hypoglycaemia is most commonly caused by accidental over administration of insulin or sulphonylureas or meglitinides. Precipitating causes include too high a dose of insulin or hypoglycaemic drug; conversely, the patient may have missed a meal or taken excessive exercise after the usual dose of insulin or oral hypoglycaemic drugs.

The signs and symptoms most commonly seen in hypoglycaemia: sweating, shaking, tachycardia as well as feeling weak, and nauseated.

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Examples of abnormal findings of glucose level:

| **Increased levels (hyperglycemia)** | **Decreased levels (hypoglycemia)** |
|---|---|
| Diabetes mellitus | Insulinoma |
| Cushing's syndrome | Starvation |
| Acromegaly | Addison's disease |
| Pheochromocytoma | Extensive liver disease |
| Acute stress response | |
| Glucagonoma | |
| Corticosteroid therapy | |

# “Blood Glucose “

## “Glucose estimation”

Principle: (Enzymatic method)

Glucose is oxidized by glucose oxidase to gluconate and hydrogen peroxide according to the following equation:

$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{GOD}} H_2O_2 + \text{Gluconate}$$

$$2H_2O_2 + \text{Phenol} + \text{4 Amino-antipyrine} \xrightarrow{\text{Peroxidase}} H_2O + \text{Quinoneimine}$$

Sample:

Serum (not hemolyzed)

Plasma

Spinal fluid

Note: Sodium fluoride is often used as preservative of whole blood to prevent glycolytic enzymes, particularly if analysis is delayed.

Note: Most laboratory instruments measure plasma glucose, but some use whole blood. Plasma glucose is 10-15% higher than whole blood glucose, since red cells contain less water per unit volume than plasma.

Normal values:

Adult FBG (70-100 mg/dl)

Adult 2 hr post prandial glucose <140 mg /dl

Note: mg/dl glucose = mmol/l × 18