Carbohydrate Metabolism Disorder

The main function of glucose is as a major tissue energy source, the energy is obtained through the pathways of glycolysis and the Krebs cycle (TCA) cycle. The brain is highly dependent upon the extracellular glucose concentration for its energy supply, hypoglycaemia is likely to impair cerebral function or even lead to irreversible neuronal damage. This is because:

1. The brain cannot synthesize glucose.
2. The brain cannot store glucose in significant amounts.
3. The brain cannot metabolize substrates other than glucose and ketones
4. The brain cannot source under physiological conditions extract enough glucose from the extracellular fluid (ECF) at low concentrations for its metabolic needs, because entry into brain cells is not facilitated by insulin.

Control of plasma glucose concentration

During normal metabolism, little glucose is lost unchanged from the body. Maintenance of plasma glucose concentrations within the relatively narrow range of 4–10 mmol/L, despite the widely varying input from the diet, depends on the balance between the glucose entering cells from the ECF and that leaving them into this compartment. Some of the more important effects of hormones on glucose homeostasis are summarized in Table (1-1).

Insulin

Insulin is the most important hormone controlling plasma glucose concentrations. A plasma glucose concentration of greater than about 5 mmol/L stimulates insulin release from the pancreas β-cell. These cells produce proinsulin, which consists of the 51-amino-acid polypeptide insulin and a linking peptide (C-peptide). Splitting of the peptide bonds by prohormone convertases releases of insulin into the ECF. Insulin binds to specific cell surface receptors and decrease blood glucose level by:

1. Enhancing the rate of glucose entry into muscle and adipose tissue.
2. Insulin induce oxidative pathways of glucose (glycolysis and pentose phosphate pathway).
3. Insulin induced activation of enzymes stimulates glucose incorporation into glycogen (glycogenesis) and inhibit glycogenolysis in liver and muscle.
4. Insulin inhibits the production of glucose (gluconeogenesis) from fats and amino acids.
5. Insulin also inhibit fat and protein breakdown (lipolysis and proteolysis).

Glucagon

Glucagon is a single-chain polypeptide synthesized by the α-cells of the pancreatic islets. Its secretion is stimulated by hypoglycaemia. Glucagon enhances hepatic glycogenolysis and gluconeogenesis.

Other hormones

When plasma insulin concentrations are low, for example during fasting, the hyperglycaemic actions of hormones, such as growth hormone (GH), glucocorticoids, adrenaline (epinephrine) and glucagon, become apparent, even if there is no increase in secretion rates. Secretion of these so-called **counter-regulatory hormones** oppose the normal action of insulin.

Table (1-1) Effects of hormones on glucose homeostasis

	Insulin	Glucagon	Growth hormone	Glucocorticoids	Adrenaline
Carbohydrate metabolism					
In liver					
Glycolysis	+				
Glycogenesis	+				
Glycogenolysis		+			+
Gluconeogenesis	–	+		+	
In muscle					
Glucose uptake	+		–	–	
Glycogenesis	+				
Glycogenolysis					+
Protein metabolism					
Synthesis	+		+		
Breakdown	–			+	
Lipid metabolism					
Synthesis	+				
Lipolysis	–		+	+	+

Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia, resulting from impairment of insulin secretion and/or action. It has been defined by the World Health Organization (WHO), on the basis of laboratory findings, diabetes mellitus can be diagnosed if a fasting plasma glucose concentration of 7.0 mmol/L or more or a random venous plasma glucose concentration of 11.1 mmol/L or more. Sometimes an oral glucose tolerance test (OGTT) 2 h after the oral ingestion of the equivalent of 75 g of anhydrous glucose, a random venous plasma glucose concentration of 11.1 mmol/L or more confirm diabetes mellitus.

Diabetes mellitus classification

1. Type 1 diabetes mellitus

Previously called insulin-**dependent** diabetes mellitus, this is the term used to describe the condition in patients for whom insulin **therapy** is essential. Patients are much more likely to develop **ketoacidosis** than type 2 diabetes. It is responsible for **10%** of the overall diabetes prevalence. It usually presents during **childhood** or adolescence. Patients with type 1 diabetes tend to be diagnosed before the age of **40 years**, are usually lean. Most of these cases are due to **immune**-mediated processes and may be associated with other autoimmune disorders such as Addison's disease. It has been suggested that many cases follow a viral infection that has damaged the β-cells of the pancreatic islets. Autoantibodies to islet cells is found in about **90%** of cases. There is a form of type 1 diabetes called idiopathic diabetes mellitus (unknown causes). Only a minority (**10%**) of patients fall into this group, which occurs mainly in individuals of African and Asian origin.

2. Type 2 diabetes mellitus

Previously called **non**-insulin-**dependent** diabetes mellitus, this is the most common variety worldwide (about **90%** of all diabetes mellitus cases). Patients are much **less** likely to develop **ketoacidosis** than those with type 1 diabetes, although insulin may sometimes be needed. Onset is most usual during **adult life**; there is a **familial** tendency and an association

with **obesity**. There is a spectrum of disorders ranging from mainly insulin **resistance** with relative insulin deficiency to a predominantly **secretory** defect with insulin resistance.

3. Other specific types of diabetes mellitus

A variety of inherited disorders may be responsible for the syndrome, either by reducing insulin secretion or by causing relative insulin deficiency because of resistance to its action or of insulin receptor defects, despite high plasma insulin concentrations.

A. Genetic defects of β-cell function: e.g. maturity-onset diabetes of the young (MODY).

B. Genetic defects of insulin action: e.g. type A insulin resistance (insulin receptor defect), for example leprechaunism and Rabson-Mendenhall syndrome.

C. Insulin deficiency due to pancreatic disease: e.g. chronic pancreatitis and pancreatectomy.

D. Endocrinopathies: e.g. acromegaly, phaeochromocytoma and Cushing's syndrome.

E. Drugs: e.g. glucocorticoids.

F. Infections: e.g. septicaemia and cytomegalovirus.

4. Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is any degree of glucose intolerance with first diagnosis during pregnancy. Gestational diabetes mellitus generally is diagnosed during the second or third trimester of pregnancy. It occurs in about 4% of pregnancies. After pregnancy ends, the glucose tolerance generally returns to normal within six weeks, at this time the woman should be reclassified. The majority of GDM patients do not develop DM but some will develop type 2 diabetes mellitus. Although it may be transient, the untreated GDM can harm the fetus or mother health. The risks to the baby consist of macrosomia (high birth weight), congenital central nervous system and cardiac irregularity. A Caesarean section may be occur if there is distinct fetal distress or an increased risk of injury coupled with macrosomia.

5. Impaired glucose tolerance

The definition of impaired glucose tolerance (IGT) is a fasting venous plasma glucose concentration of less than 7.0 mmol/L and a plasma glucose concentration between

7.8 mmol/L and 11.1 mmol/L 2 h after an OGTT. Some patients with IGT develop diabetes mellitus later.

6. Impaired fasting glucose

Impaired fasting glucose (IFG), like IGT, refers to a metabolic stage intermediate between normal glucose homeostasis and diabetes mellitus. The definition is that the fasting venous plasma glucose is 6.1 mmol/L or more but less than 7.0 mmol/L, and less than 7.8 mmol/L 2 h after an OGTT.

Metabolic features of diabetes mellitus

1. Hyperglycaemia

If plasma glucose concentration exceeds about 10 mmol/L, glycosuria would be expected. High urinary glucose concentrations produce an osmotic diuresis and therefore **polyuria**. Cerebral cellular dehydration due to hyperosmolality, secondary to hyperglycaemia, causes thirst (**polydipsia**). A prolonged osmotic diuresis may cause excessive urinary electrolyte loss. These 'classic' symptoms are suggestive of diabetes mellitus. The decreasing of insulin level lead to decrease the entrance of glucose to cells, this lead to decrease the intracellular energy and increase the hunger **(polyphagia)**.

2. Abnormalities in lipid metabolism

These may be secondary to insulin deficiency. **Lipolysis** is enhanced and plasma **fatty acids** concentrations rise. In the liver, fatty acids are converted to **acetyl CoA** and **ketones**, or are reesterified to form endogenous **triglycerides** and incorporated into **VLDLs**; the latter accumulate in plasma because inhibition of lipoprotein lipase, which is necessary for VLDL catabolism, insulin stimulate lipoprotein lipase. **HDL** concentration tends to be low in type 2 diabetes. If insulin deficiency is very severe, there may also be **chylomicronaemia**. The rate of **cholesterol** synthesis is also increased, with an associated increase in plasma **LDL** concentrations. Consequently, patients with diabetes may show high plasma triglyceride, raised cholesterol and low HDL cholesterol concentrations.

Long term effects of diabetes mellitus

Vascular disease is a common complication of diabetes mellitus. **Macrovascular disease** due to abnormalities of large vessels may present as coronary artery, cerebrovascular or peripheral vascular insufficiency. The condition is probably related to alterations in lipid metabolism and associated hypertension. The most common cause of death is cardiovascular disease, including myocardial infarction. **Microvascular disease** due to abnormalities of small blood vessels particularly affects the retina (**retinopathy**) and the kidney (**nephropathy**); both may be related to inadequate glucose control. Kidney disease is associated with several abnormalities, including **proteinuria** and progressive renal failure. The presence of small amounts of albumin in the urine (**microalbuminuria**) is associated with an increased risk of developing progressive renal disease. The renal complications may be partly due to the increased **glycation** of structural proteins in the arterial walls supplying the glomerular basement membrane; similar vascular changes in the retina may account for the high incidence of diabetic retinopathy. Diabetic **neuropathy** can occur. It has been suggested that sorbitol is implicated in the aetiology of diabetic neuropathy through the action of aldolase reductase. **Diabetic ulcers**, for example of the feet, can lead to gangrene and amputation. The ulcers can be **ischaemic**, **neuropathic** or **infective**.

Acute metabolic complications of diabetes mellitus

1. 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 hypoglycaemic drug, the patient may have missed a meal or taken excessive exercise after the usual dose of insulin or oral hypoglycaemic drugs.

2. Diabetic ketoacidosis (DKA)

In the absence of insulin, there is increased lipid and protein breakdown, enhanced hepatic gluconeogenesis and impaired glucose entry into cells. Plasma glucose concentrations are usually in the range **20-40 mmol/L**, **hyperglycaemia** causes **glycosuria** and hence an osmotic diuresis. There may be haemoconcentration and reduction of the glomerular

filtration rate enough to cause **uraemia** due to renal circulatory insufficiency. The extracellular hyperosmolality causes a shift of water out of the cellular compartment and severe cellular **dehydration** occurs. Loss of water from cerebral cells is probably the reason for the **confusion** and **coma**. Thus there is both cellular and extracellular volume depletion.

The rate of **lipolysis** is increased because of decreased insulin activity; more free fatty acids are produced than can be metabolized by peripheral tissues. Most tissues, other than the brain, can oxidize fatty acids to acetyl CoA, which can then be used in the TCA cycle as an energy source. When the rate of synthesis exceeds its use, the hepatic cells produce acetoacetic acid by enzymatic condensation of two molecules of acetyl CoA; acetoacetic acid can be reduced to β-hydroxybutyric acid and decarboxylated to acetone. When the rate of formation of ketone bodies is greater than the rate of their use, their levels begin to rise in the blood (**ketonemia**) and, eventually, in the urine (**ketonuria**). This is seen most often in cases of uncontrolled, **type 1 diabetes mellitus**.

Hydrogen ions produced with ketones are buffered by plasma bicarbonate. However, when their rate of production of ketones exceeds the rate of bicarbonate generation, the plasma **bicarbonate** falls and this lead to fall in plasma **pH** (**metabolic acidosis**). The deep, sighing respiration (**Kussmaul's respiration**) and the odour of acetone on the breath are classic features of diabetic ketoacidosis.

Plasma potassium concentrations may be raised (**hyperkalaemia**), secondarily to the metabolic acidosis. This is due to failure of glucose entry into cells in the absence of insulin and because of the low glomerular filtration rate. Plasma sodium concentrations may be low (**hyponatraemia**) because of the osmotic effect of the high extracellular glucose concentration, which draws water from the cells and dilutes the sodium. Hyperphosphataemia followed by hypophosphataemia as plasma phosphate concentrations parallel those of potassium may persist for several days after recovery from diabetic coma. Similarly, hypermagnesaemia can result, partly because of the acidosis.

3. Hyperosmolal non-ketotic coma (HONK)

The term ‘hyperosmolal’ coma is usually confined to a condition in which there is marked hyperglycaemia but no detectable ketoacidosis. The reason for these different presentations is not clear. It has been suggested that insulin activity is sufficient to suppress lipolysis but insufficient to suppress hepatic gluconeogenesis or to facilitate glucose transport into cells. HONK is more common in **older** patients. Plasma glucose concentrations may exceed **50 mmol/L**. The effects of **glycosuria** are as described above, but **hypernatraemia** due to predominant water loss is more commonly found than in ketoacidosis and aggravates the plasma hyperosmolality. Cerebral cellular dehydration is probably the reason for the **confusion** and **coma**. This is seen most often in cases of uncontrolled, **type 2 diabetes mellitus**.

Monitoring of diabetes mellitus

1. Glycosuria

Glycosuria can be defined as a concentration of urinary glucose. This test insensitive, but specific, it occurs only when the plasma, and therefore glomerular filtrate, concentrations exceed the tubular reabsorptive capacity. This may be because the plasma and glomerular filtrate concentrations are more than about 10 mmol/L, and therefore the normal tubular reabsorptive capacity is significantly exceeded. A diagnosis of diabetes mellitus should never be made on the basis of glycosuria because if the glomerular filtration rate is much reduced, there may be no glycosuria despite plasma glucose concentrations more than 10 mmol/L.

2. Blood glucose

The standard ways used for diagnosis of DM which are based on values of fasting blood glucose, random blood glucose and OGTT. Blood glucose concentrations more accurately based on these results than on those obtained by testing their urine. This method of testing is also useful in the detection of hypoglycaemia (urinary glucose testing can cannot detect hypoglycaemia because it depende on the renal glucose threshold).

3. 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. Measurement of blood HbA1c 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 HbA1c, the poorer the mean diabetic or glycaemic control.

4. Fructosamine

The measurement of plasma fructosamine concentrations may be used to assess glucose control over a shorter time course than that of HbA1c (about 2-4 weeks), but the assay has methodological limitations. Fructosamine reflects glucose bound to plasma proteins, predominantly albumin, which has a plasma half-life of about 20 days but is problematic in patients with hypoalbuminaemia, for example due to severe proteinuria.

5. Blood ketones

Monitoring of blood ketones may have a place in the home management of type 1 diabetes.

6. Urinary albumin determination and diabetic nephropathy

One of the earliest signs of diabetic renal dysfunction is the development of small amounts of albumin in the urine, called microalbuminuria. Untreated, this can progress to overt albuminuria or **proteinuria** (more than 300 mg/day), impaired renal function and finally end-stage renal failure. **Microalbuminuria** is defined as a urinary albumin excretion of 30-300 mg/day. An albumin concentration less than 30 mg/day is defined as **normoalbuminuria**. Apart from being predictive of diabetic renal complications, urinary albumin excretion is also associated with increased vascular permeability and enhanced risk of cardiovascular disease.

Hypoglycaemia

Hypoglycaemia is present if the plasma glucose concentration is less than 2.5 mmol/L. Early symptoms of hypoglycaemia (**adrenargic** symptoms) may develop when adrenaline secretion is stimulated and may cause **sweating**, **tachycardia** and **agitation**. Cerebral symptoms (**neuroglycopenia**) resulted from inadequate supply of glucose from ECF cerebral tissue, and the symptoms of hypoglycaemia are **faintness**, **dizziness** or **lethargy** may progress rapidly to **coma** and, if untreated, permanent cerebral damage or **death** may occur.

Hypoglycaemia classification

1. Hypoinsulinaemic hypoglycaemia

A. Non-pancreatic tumours (non-islet cell tumours)

Carcinomas (especially of the liver) and sarcomas have been reported to cause hypoglycaemia. The mechanism is not always clear, but may sometimes be due to the secretion of insulin-like growth factor 2 (IGF-2) or abnormal glycosylated big IGF-2. The IGF-2 suppresses GH and IGF-1. Tumours secreting IGF-2 are characterized by an increased plasma total IGF-2:IGF-1 ratio and low plasma insulin concentration.

B. Endocrine causes

Hypoglycaemia may occur in hypothyroidism, pituitary or adrenal insufficiency.

C. Impaired liver function

The functional reserve of the liver is so great that, despite its central role in the maintenance of plasma glucose concentrations, hypoglycaemia is a rare complication of liver disease. It may complicate very severe hepatitis, hypoxic liver disease or liver necrosis if the whole liver is affected.

D. Renal failure

Renal failure can result in hypoglycaemia because the kidney is a gluconeogenic organ.

2. Hyperinsulinaemic hypoglycaemia

Exogenous insulin or other drugs such as sulphonylureas or meglitinides are probably the most common causes of hyperinsulinaemic hypoglycaemia. Pancreatic tumour (insulinoma) is another cause. One of the most important tests in a patient with proven hypoglycaemia is

to measure the plasma insulin and C-peptide concentrations when the plasma glucose concentration is low. Measurement of plasma C-peptide concentrations may help to differentiate between exogenous insulin administration from endogenous insulin secretion.

Raised plasma insulin concentrations and suppressed plasma concentrations of C-peptide suggest exogenous insulin administration while raised plasma insulin concentrations and increased plasma concentrations of C-peptide suggest endogenous insulin secretion resulted from an insulinoma or following pancreatic stimulation by sulphonylurea drugs. To differentiate between endogenous insulin secretion resulted from an insulinoma or from sulphonylurea drugs, urine or plasma drug screen is thus important.

3. Reactive (functional) hypoglycaemia

Some people develop symptomatic hypoglycaemia between 2 and 4 h after a meal or a glucose load. When rapid passage of glucose into the intestine, and rapid absorption, may stimulate excessive insulin secretion (‘late dumping syndrome’).

Alcohol-induced hypoglycaemia

Hypoglycaemia may develop between 2 and 10 h after the ingestion of large amounts of alcohol. Hypoglycaemia is probably caused by the suppression of gluconeogenesis during the metabolism of alcohol.