Disorders of CHO metabolim

By
Dr.Qutaiba Alhajjaj
Ph.D Clinical Biochemistry

Topics

- Regulation of blood glucose .
- Diabetes mellitus
- Hypoglycemia

Functions of extracellular glucose

- The main function of glucose is a major tissue energy source (glycolysis and the Krebs cycle).

- The brain is highly dependent upon the extracellular glucose concentration for its energy supply (about 60% of whole body utilization) ; therefore; hypoglycaemia is likely to impair cerebral function or even lead to irreversible neuronal damage. This is because the brain :

- Cannot synthesize glucose

Functions of extracellular glucose

- Cannot store glucose in significant amounts,
- Cannot metabolize substrates other than glucose and ketones

-plasma ketone concentrations are usually very low and ketones are of little importance as an energy source under physiological conditions,

- Cannot 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.

Functions of extracellular glucose

- Normally the plasma glucose concentration remains between about 4 mmol/L and 10 mmol/L , despite the intermittent load entering the body from the diet.

- The maintenance of plasma glucose concentrations below about 10 mmol/L minimizes loss from the body as well as providing the optimal supply to the tissues.

Regulation of plasma glucose concentration

- Insulin is the most important hormone controlling plasma glucose concentrations.
- A plasma glucose concentration of greater than about 5 mmol/L acting via the glucose transporter 2 stimulates insulin release from the pancreas b-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 insulin and C-peptide into the ECF

Actions of Insulin

- Insulin binds to specific cell surface receptors on muscle and adipose tissue, thus enhancing the rate of glucose entry into these cells.

- Insulin-induced glycogenesis in liver and muscle.

- Insulin inhibits gluconeogenesis from fats and amino acids, partly by inhibiting fat and protein breakdown (lipolysis and proteolysis).

Actions of Insulin

- The transport of glucose into liver cells is insulin independent but, by reducing the intracellular glucose concentration, insulin does indirectly promote the passive diffusion of glucose into them.

Counter-regulatory hormones

- Such as growth hormone (GH), glucocorticoids, adrenaline (epinephrine) and glucagon .

- Increase during fasting , stress and in patients with acromegaly (GH), Cushing's syndrome (glucocorticoids) or in phaeochromocytoma (adrenaline and noradrenaline) and thus oppose the normal action of insulin.

liver

- The liver is the most important organ maintaining a constant glucose supply for other tissues, including the brain. It is also of importance in controlling the postprandial plasma glucose concentration.

- The entry of glucose into liver and cerebral cells is not directly affected by insulin, but depends on the extracellular glucose concentration.

Glucokinase and hexokinase

- The conversion of glucose to glucose-6-phosphate (G6P), the first step in glucose metabolism in all cells, is catalysed in the liver by the enzyme glucokinase, which has a low affinity for glucose compared with that of hexokinase, which is found in most other tissues.

- Glucokinase activity is induced by insulin. Therefore, hepatic cells extract proportionally less glucose during fasting, when concentrations in portal venous plasma are low, than after carbohydrate ingestion. This helps to maintain a fasting supply of glucose to vulnerable tissues such as the brain.

liver

- The liver cells can store some of the excess glucose as glycogen. The rate of glycogen synthesis (glycogenesis) from G6P may be increased by insulin secreted by the b-cells of the pancreas in response to systemic hyperglycaemia.

- The liver can convert some of the excess glucose to fatty acids, which are ultimately transported as triglyceride in very low-density lipoprotein (VLDL) and stored in adipose tissue.

liver

- During fasting, the liver converts fatty acids, released from adipose tissue as a consequence of low insulin activity, to ketones.

- The carbon chains of some amino acids may also be converted to ketones . Ketones can be used by other tissues, including the brain, as an energy source when plasma glucose concentrations are low.

Other organs

- The renal cortex is the only other tissue capable of gluconeogenesis, and of converting G6P to glucose. The gluconeogenic capacity of the kidney is particularly important in hydrogen ion homeostasis and during prolonged fasting.

- Other tissues, such as muscle, can store glycogen but, because they do not contain glucose-6-phosphatase, they cannot release glucose from cells and so can only use it locally; this glycogen plays no part in maintaining the plasma glucose concentration.

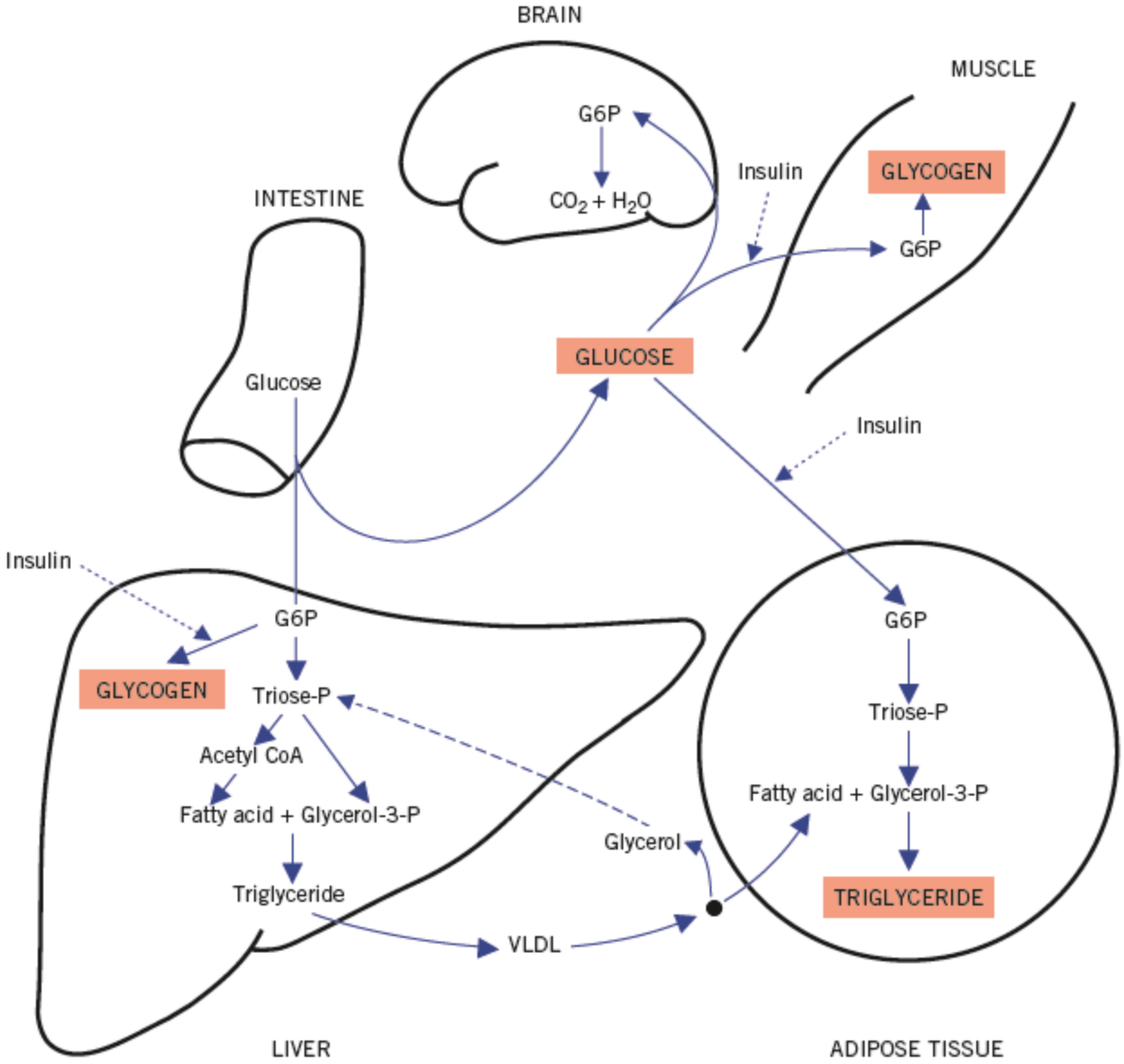


Figure 12.5 Post-prandial metabolism of glucose. CoA, coenzyme A; G6P, glucose-6-phosphate; Glycerol-3-P, glycerol-3-phosphate; Triose-P, triose phosphate or glyceraldehyde 3-phosphate; VLDL, very low-density lipoprotein

glucose concentrations. during childhood, ketotic hypoglycaemia may occur. The

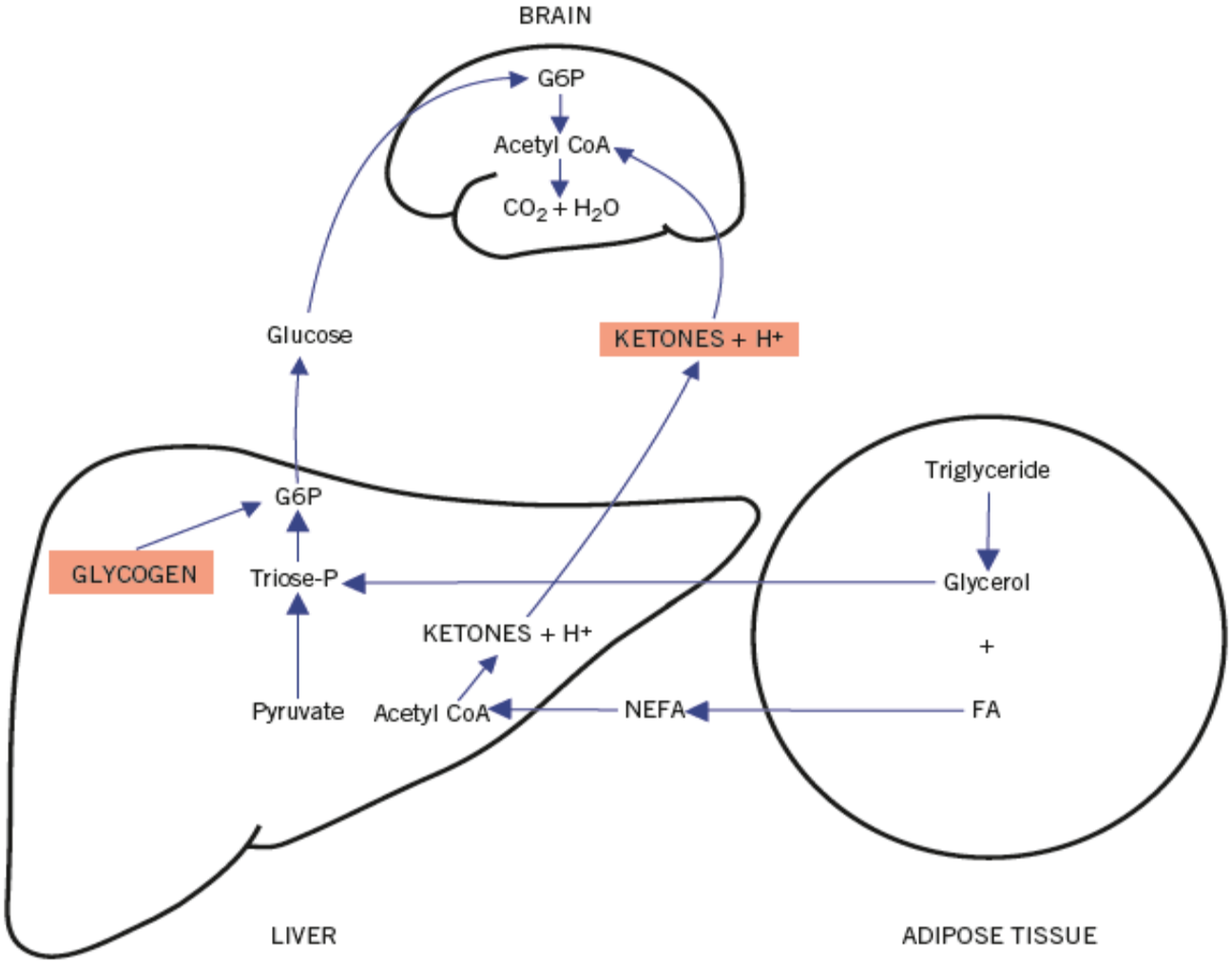


Figure 12.6 Intermediary metabolism during fasting: ketosis. CoA, coenzyme A; FA, fatty acid; G6P, glucose-6-phosphate; NEFA, non-esterified fatty acid.

PHYSIOLOGICAL AND PATHOLOGICAL LATIC ACIDOSIS

- Cori cycle .
- Lactic acid, produced by anaerobic glycolysis, may either be oxidized to CO_2 and water in the TCA cycle or be re-converted 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:

Tissue hypoxia

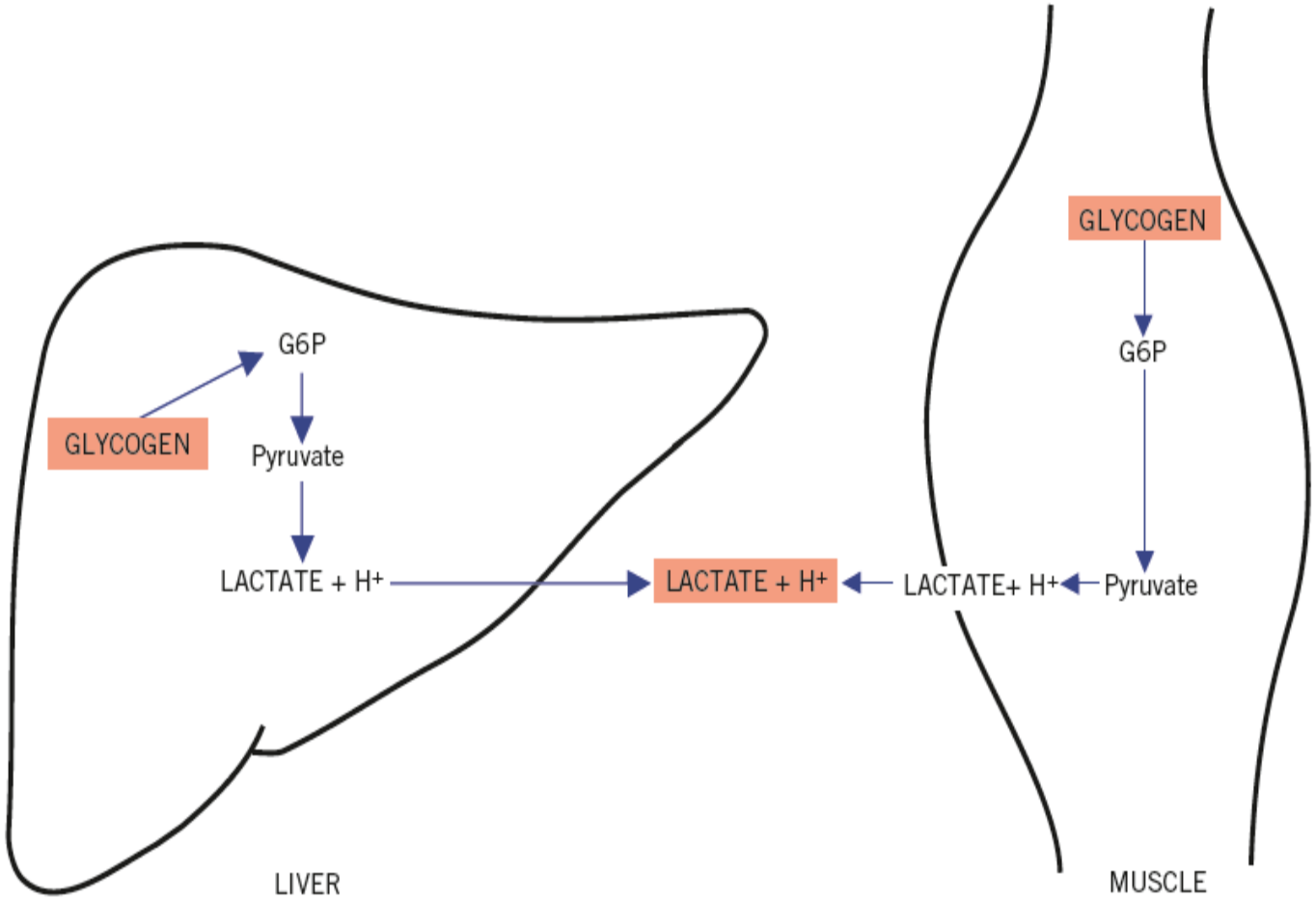


Figure 12.8 Metabolic pathways during tissue hypoxia. G6P, glucose-6-phosphate.

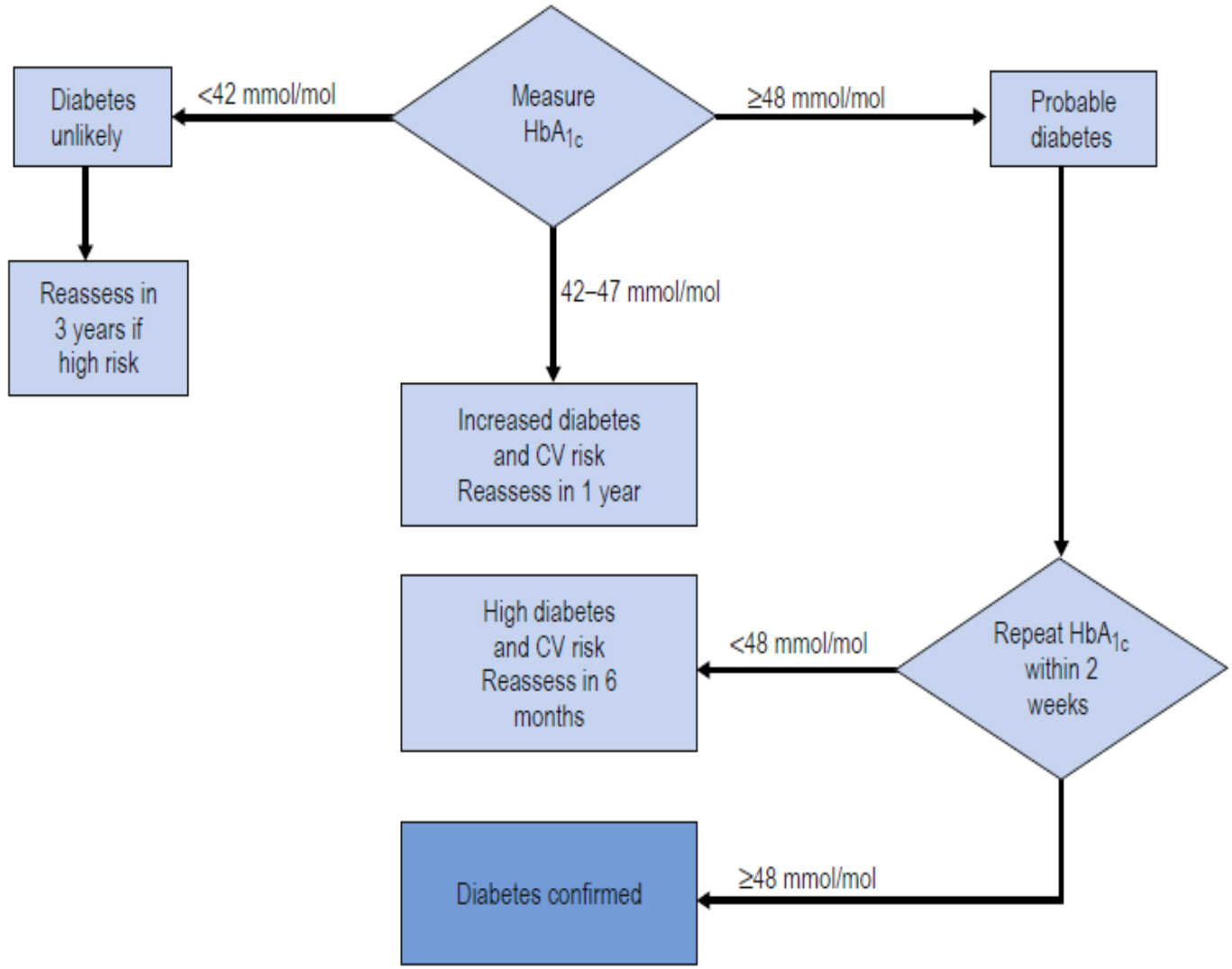
HYPERGLYCAEMIA AND DIABETES MELLITUS

- Diabetes mellitus is caused by an absolute or relative insulin deficiency and /or insulin resistance.
- It has been defined by the World Health Organization (WHO), on the basis of laboratory findings, as a fasting plasma glucose of 7.0 mmol/L or more (on more than one occasion or once in the presence of diabetes symptoms)
- or a random plasma glucose of 11.1 mmol/L or more ,
- or HbA1c ≥ 6.5 % . Sometimes an oral glucose tolerance test (OGTT) may be required to establish the diagnosis in equivocal cases.

HbA1c in diagnosis

HbA1c	mmol/mol	%
Normal	**Below 42 mmol/mol**	**Below 6.0%**
Prediabetes	42 to 47 mmol/mol	6.0% to 6.4%
Diabetes	48 mmol/mol or over	6.5% or over

HbA1c mmol/mol (new units)	HbA1c % (old units)	Estimated average glucose mmol/L
42	6	6.9
53	7	8.5
64	8	10.2
75	9	11.8
86	10	13.3
97	11	14.9
108	12	16.5
119	13	18.1



HbA_{1c} may be used to diagnose diabetes mellitus in patients with long-standing hyperglycaemia

HbA_{1c} may be used to diagnose diabetes mellitus in patients with long-standing hyperglycaemia

HbA_{1c} must not be used for diagnosis if hyperglycaemia has developed rapidly, e.g.

- possible type 1 diabetes
- symptomatic children and young adults
- symptoms less than three months
- acutely ill patients
- drugs that may cause rapid rise in glucose e.g. corticosteroids, antipsychotics
- acute pancreatic damage or pancreatic surgery.

HbA_{1c} must not be used for diagnosis in the presence of factors affecting HbA_{1c} formation or measurement. These include:

- iron and vitamin B_{12} deficiency
- haemolytic anaemias
- chronic liver disease
- chronic kidney disease (CKD 4 and 5)
- splenomegaly or splenectomy
- haemoglobinopathies.

HbA_{1c} must not be used to diagnose diabetes in pregnancy

Fig. 13.4 The use of glycated haemoglobin (HbA_{1c}) in the diagnosis of diabetes. CV, cardiovascular disease.

clinical entity in itself. In some patients it is a transitory stage between normal glucose tolerance and diabetes; in others it is a stable state (often associated with obesity). Both IFG and IGT reflect abnormal glucose metabolism and are associated with increased risk of cardiovascular disease and of future development of type 2 DM. Patients should be given dietary and lifestyle advice and followed up regularly.

Notably, measurements of plasma glucose are no exception to the potential for analytical and biological variation to affect results (see Chapter 2). Although precise figures

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 because they are prone to develop ketoacidosis.

- It usually presents during childhood or adolescence. Most of these cases are due to immune-mediated processes and may be associated with other autoimmune disorders such as Addison's disease, vitiligo and Hashimoto's thyroiditis.

- It has been suggested that many cases follow a viral infection that has damaged the b-cells of the pancreatic islets.

Type 2 diabetes mellitus

- Previously called non-insulin-dependent diabetes mellitus, this is the most common variety worldwide (about 90 per cent 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

Other specific types of Diabetes

- Gestational diabetes mellitus
- *Genetic defects of* b-*cell function including :*
- Maturity-onset diabetes of the young (MODY):
  - MODY 1: mutation of the hepatocyte nuclear factor (*HNF4A*) gene,
  - MODY 2: mutation of the glucokinase gene,
  - MODY 3: mutation of the *HNF1A* gene

Impaired glucose tolerance

- The WHO 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.

Impaired fasting glucose

- 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.

Subjects at risk of developing diabetes mellitus

1-Strong family history of diabetes mellitus

2-Autoimmune disease

3-Obesity

4-Sedentary life style

5-Gestational diabetes

6-Prediabetes

7-Age over 45 years

8-Stress

Metabolic features of diabetes mellitus

- Patients with type 1 diabetes tend to be diagnosed before the age of 40 years, are usually lean and have experienced weight loss at the time of presentation.

- They may present with diabetic ketoacidosis. Conversely, patients with type 2 diabetes often present later, usually after the age of 40 years, and are often overweight or obese.

Long-term effects of diabetes mellitus

1-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.

Long-term effects of diabetes mellitus

2-Microvascular disease due to abnormalities of small blood vessels particularly affects the retina (diabetic retinopathy) and the kidney (nephropathy); both may be related to inadequate glucose control.

3-Infections

4-Diabetic ulcers

Monitoring of diabetes mellitus

1-Glycosuria

2-Blood glucose

3-Glycated haemoglobin (HbA1c) gives a retrospective assessment of the mean plasma glucose concentration during the preceding 6–8 weeks.

4-*Fructosamine* assess glucose control over a shorter time course than that of HbA1c (about 2–4 weeks

Monitoring of diabetes mellitus

5-*Blood ketones*

6-Urinary albumin

Acute metabolic complications of diabetes mellitus

1-*Hypoglycaemia*

2-*Diabetic ketoacidosis*

3-*Hyperosmolal non-ketotic coma(HONK)*

4-*Lactic acidosis*

and the odour of acetone on the breath are classic features of diabetic ketoacidosis.

Plasma potassium concentrations may be raised, secondarily to the metabolic acidosis, before treatment is started. This is due to failure of glucose entry into cells in the absence of insulin and because of the low glomerular filtration rate. Despite hyperkalaemia, there is a total body deficit due to increased urinary potassium loss in the presence of an osmotic diuresis. During treatment, plasma potassium concentrations may fall as potassium re-enters cells, sometimes causing severe hypokalaemia unless potassium is prescribed.

Plasma sodium concentrations may be low (hyponatraemia) or low-normal at presentation, partly because of the osmotic effect of the high extracellular glucose concentration, which draws water from the cells and dilutes the sodium. In the presence of a very high plasma glucose concentration, a normal or raised plasma sodium concentration is suggestive of significant water depletion.

If there is severe hyperlipidaemia, the possibility of pseudohyponatraemia must be considered (see Chapter

Table 12.4 Clinical and biochemical findings in a patient presenting with diabetic ketoacidosis

Findings	Underlying abnormality
Clinical	
Confusion and later coma	Hyperosmolality
Hyperventilation (Kussmaul's respiration)	Metabolic acidosis
Signs of volume depletion	Osmotic diuresis
Biochemical	
Plasma	
Hyperglycaemia	Insulin deficiency
Low plasma bicarbonate	Metabolic acidosis
Initial hyperkalaemia	Intracellular potassium moves out
Mild uraemia	Decreased glomerular filtration rate
Urine	
Glycosuria	Insulin deficiency
Ketonuria	Insulin deficiency

Investigation of suspected diabetes mellitus

Diabetes mellitus is confirmed if one of the following is present:

a fasting venous plasma concentration of 7.0 mmol/L or more on two occasions or once with symptoms, or

a random venous plasma concentration of

11.1 mmol/L or more on two occasions or once with symptoms.

Table 12.6 Interpretation of the oral glucose tolerance test (glucose mmol/L); venous plasma preferred

	Venous plasma		Capillary whole blood		Venous whole blood	
	Fasting	2 h	Fasting	2 h	Fasting	2 h
Diabetes mellitus unlikely	<6.1	<7.8	<5.6	<7.8	<5.6	<6.7
Impaired glucose tolerance	<7.0	7.8–11.1	<6.1	7.8–11.1	<6.1	6.7–10.0
Impaired fasting glucose	6.1–6.9	<7.8	5.6–6.0	<7.8	5.6–6.0	<6.7
Diabetes mellitus	≥7.0	≥11.1	≥6.1	≥11.1	≥6.1	≥10.0

values' may not be applicable. This may be due to a circadian variation in islet cell responsiveness.

- *Drug* Steroids, oral contraceptives and thiazide diuretics may impair glucose tolerance.

HYPOGLYCAEMIA (FIG. 12.9)

Symptoms of hypoglycaemia may develop at higher concentrations if there has been a rapid fall from a previously raised value, when adrenaline secretion is stimulated and may cause sweating, tachycardia and agitation. As discussed earlier, cerebral metabolism depends on an adequate supply of glucose from ECF

HYPOGLYCAEMIA

if the plasma glucose concentration is less than 2.5 mmol/L in a specimen collected into a tube containing an inhibitor of glycolysis, for example fluoride oxalate.

Blood

cells continue to metabolize glucose in vitro, and low concentrations found in a specimen collected without such an inhibitor can be dangerously misleading (pseudohypoglycaemia).

Hyperinsulinaemic hypoglycaemia

Inappropriately high insulin concentrations due to:
Pancreatic tumour – insulinoma
Hyperplasia of the pancreatic islet cells
Insulin receptor antibodies
Autoimmune insulin syndrome
Exogenous insulin
Sulphonylureas, meglitinides

Hypoinsulinaemic hypoglycaemia

1-Endocrine : Glucocorticoid deficiency/adrenal insufficiency , Severe hypothyroidism ,Hypopituitarism

2-organ failure : Severe liver disease , End-stage renal disease , Severe congestive cardiac failure

3-Some non-pancreatic islet cell tumours Insulin-like growth factor (IGF)-2-secreting tumours, e.g. liver, adrenal, breast, Leukaemias, lymphomas

Reactive hypoglycaemia

Idiopathic

Post-gastric surgery

Alcohol induced

Miscellaneous causes

Von Gierke's disease (type 1 glycogen storage disease)

Drugs, e.g. salicylates, quinine, haloperidol, pentamidine, sulphonamides

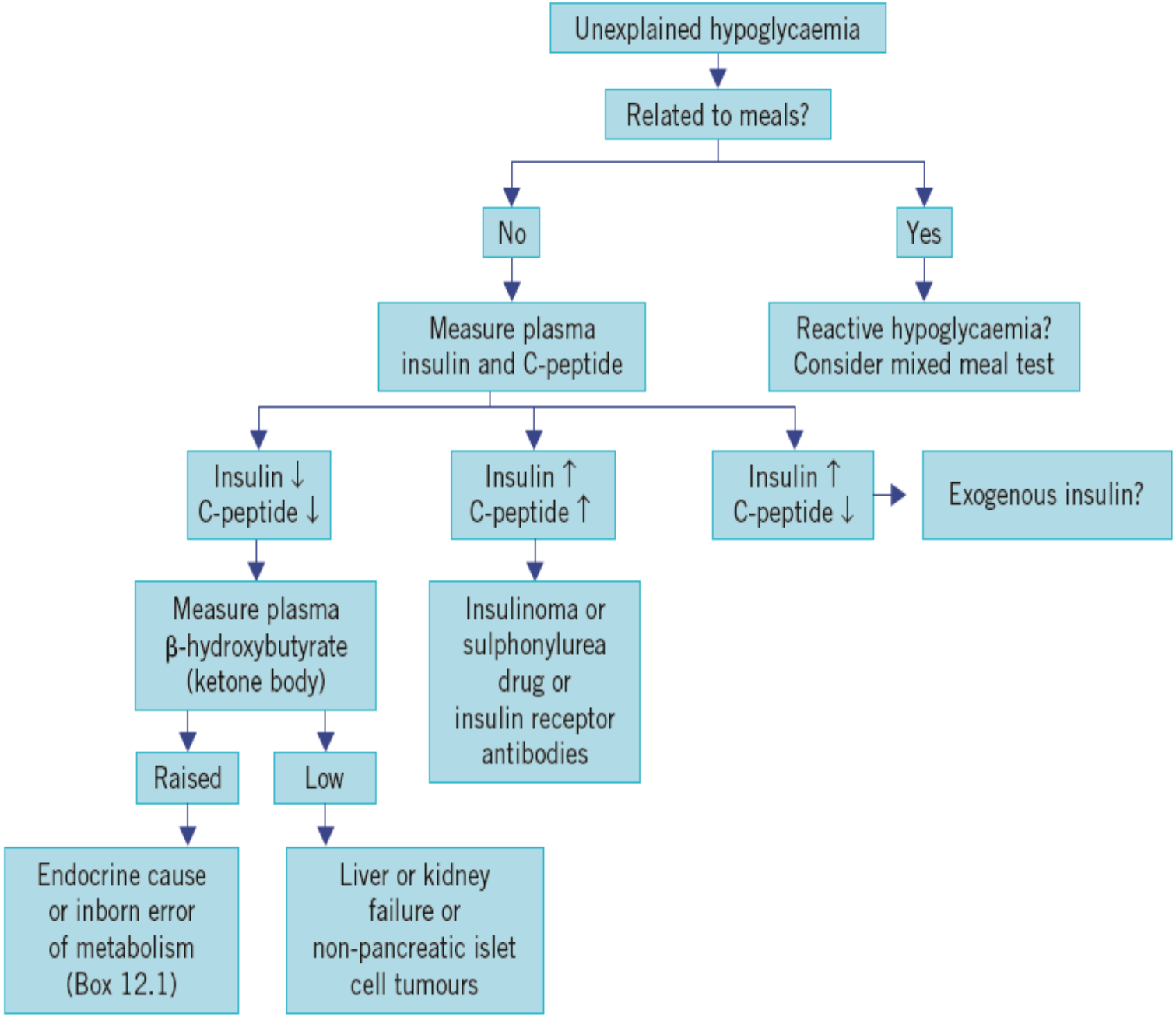


Figure 12.9 Algorithm for the investigation of hypoglycaemia in adults.

SUMMARY

- Diabetes mellitus is a common medical condition, and an understanding of its biochemistry aids its medical management. Type 1 diabetes mellitus is associated with insulin deficiency and may present with weight loss and urinary ketones in young individuals. There is a relationship with autoimmune disease. Treatment is with insulin. Conversely, type 2 diabetes mellitus is usually associated with insulin resistance, increased body weight and later age presentation. There may be a family history of diabetes mellitus. Treatment involves diet and biguanides, sulphonylureas, glitazones or incretins, although insulin may sometimes be needed.
- Biochemical tests have a major role in the management of diabetes mellitus and in monitoring its complications, such as in the control of blood glucose, HbA_{1c}, plasma lipids and urinary ACR.
- Diabetes mellitus can present with various comas, including hypoglycaemia, diabetic ketoacidosis (type 1), HONK and lactic acidosis.
- Hypoglycaemia can present with neurological impairment and coma. A useful classification is to divide hypoglycaemia into that with high plasma insulin and that with low insulin levels. The causes of hyperinsulinaemic hypoglycaemia include insulinomas and following insulin administration. The causes of hypoinsulinaemic hypoglycaemia include severe hepatic disease, adrenal insufficiency, pituitary failure and non-pancreatic tumours producing insulin-like substances.

References

1-*Clinical Biochemistry & Metabolic Medicine by Martin A Crook , eighth edition 2012 .*

2-Clinical Chemistry by William J Marshall , ninth edition 2021

END OF LECTURE

THANKS FOR LISTENING