Diabetes Mellitus

Diabetes mellitus is the most common of the endocrine disorders. It is a chronic metabolic condition, characterised by hyperglycaemia (due to impaired insulin production and secretion with or without insulin resistance and abnormalities in carbohydrate, fat, and protein metabolism. Diabetes mellitus may be classified according to aetiology, by far the most common types being type 1 and type 2 diabetes

Type 1 diabetes is a disease characterised by the destruction of the insulin-producing pancreatic β-cells. In more than 90% of cases, β-cell destruction is associated with autoimmune disease. Type 1 diabetes usually develops in children or young adults, although it can develop at any age and is associated with a faster onset of symptoms, leading to dependency on extrinsic insulin for survival.

Type 2 diabetes is more common and traditionally occurs in adults older than 40 years, with a peak onset between 60 and 70 years of age in developed countries. Regrettably, it is being increasingly seen in younger people, including adolescents and children.

Aetiology

Type 1 diabetes, both genetic and environmental factors are relevant in its development. Circulating islet cell antibodies (ICAs) are present in 70–90% of those with type 1 at the time of diagnosis. The appearance of ICAs often precedes the onset of clinical diabetes by several years. The final event that precipitates clinical diabetes may be caused by sudden stress, such as an infection when the mass of β-cells in the pancreas falls to less than 5–10%, but more usually is unknown.

Type 2 diabetes has a stronger genetic predisposition. Identical twins have a concordance rate approaching 100%, suggesting the relative importance of inheritance over environment. If a parent has type 2, the risk of a child eventually developing type 2 is 15%, increasing to 50% if both parents, compared with 2–6% for type 1. Type 2 diabetes occurs because of the progressive development of insulin resistance and β-cell dysfunction, the latter leading to an inability of the pancreas to produce enough insulin to overcome the insulin resistance. About 80% of people with type 2 diabetes are obese. This highlights the clear association between type 2 and obesity, with obesity causing insulin resistance. In particular, central obesity, where adipose tissue is deposited intra-abdominally rather than subcutaneously, is associated with the highest risk. Body mass index (BMI) has been used as an indicator for predicting type 2 risk; however, it does not take fat distribution into account, so waist circumference measurements are more reliable and are now being increasingly used.

Table 45.1 Differences between type 1 and type 2 diabetes

Type 1 diabetes	Type 2 diabetes
Autoimmune-mediated β-cell destruction	No autoimmune-mediated β-cell destruction
Islet cell antibodies present	No islet cell antibodies present
Genetic link	Very strong genetic link
Age of onset usually younger than 30 years	Age of onset usually older than 40 years
Faster onset of symptoms	Slower onset of symptoms
Insulin must be administered	Diet control and oral hypoglycaemic agents often sufficient control
Patients usually not overweight	Patients usually overweight
Extreme hyperglycaemia causes diabetic ketoacidosis	Extreme hyperglycaemia causes hyperosmolar hyperglycaemic state

Pathophysiology

Glucose is the major stimulant to insulin release. The response is triggered both by the intake of nutrients and the release of gastro-intestinal peptide hormones. After an intravenous injection of glucose, there is a biphasic insulin response. There is an initial rapid response in the first 2 minutes, followed after 5–10 minutes by a second response which is smaller but sustained over 1 hour. The initial response represents the release of stored insulin, and the second phase reflects discharge of newly synthesised insulin. Glucose is unique; other agents, including sulfonylureas, do not result in insulin biosynthesis, only release. Once released from the pancreas, insulin enters the portal circulation. The liver rapidly degrades it, and only 50% reaches the peripheral circulation. In the basal state, insulin secretion is at a rate of approximately 1 unit/h. The intake of food results in a prompt 5- to 10-fold increase in insulin release. Total daily secretion of insulin into the circulation in healthy individuals ranges from 30 to 50 units.

In type 1 diabetes, there is an acute deficiency of insulin that leads to unrestrained hepatic glycogenolysis and gluconeogenesis with a consequent increase in hepatic glucose output. Also,

glucose uptake is decreased in insulin-sensitive tissues such as adipose tissue and muscle; hence, hyperglycaemia ensues. Either as a result of the metabolic disturbance itself or secondary to infection or other acute illness, there is increased secretion of the counter-regulatory hormones glucagon, cortisol, catecholamines and growth hormone. All of these will further increase hepatic glucose production.

In type 2 diabetes, the process is usually less acute because relative insulin deficiency decreases over a sustained period of time. The initial response to hyperglycaemia is increased insulin production enabling euglycaemia. This hyperinsulinemia is able to maintain glucose levels for a period of time, but as insulin resistance increases, eventually not enough insulin can be produced, and β-cell function deteriorates, leading to a relative deficiency in insulin, and hyperglycaemia ensues. If this cycle is not interrupted, type 2 diabetes develops. Impaired glucose tolerance (IGT), impaired fasting glucose or hyperinsulinemia may be detected before overt diabetes develops, and if so, a strict diet and exercise regimen leading to weight loss and improved insulin sensitivity may delay or even prevent the onset of diabetes. At the time of diagnosis, those with type 2 diabetes may have already lost about 50% of their β-cell function. Irrespective of treatment, β-cell function continues to decline with time, often leading to the need for exogenous insulin therapy.

Pathophysiology of insulin resistance

- Abdominal fat is metabolically different from subcutaneous fat due to excess lipids in non-adipose tissue, which leads to cell dysfunction and death and subsequently lipotoxicity. Abdominal fat is resistant to the antilipolytic effects of insulin result in release of excessive amounts of free fatty acids, leading to insulin resistance in the liver and muscle. The effect is an increase in gluconeogenesis in the liver and an inhibition of insulin-mediated glucose uptake in the muscle.
- Excess fat make adipocytes become too large, and thus unable to store additional fat leading to fat storage in the muscles, liver and pancreas, and finally causing insulin resistance in these organs.
- Adipose tissue causes the oversecretion of some cytokines like:
- Plasminogen activator inhibitor-1 (which is prothrombotic),
- Tumour necrosis factor-α and interleukin-6 (which are proinflammatory)
- Resistin (which causes insulin resistance).
- Excess adipose tissue cause undersecretion of a beneficial adipokine (adiponectin).

Adiponectin is a protein (adipokines), which is involved in regulating glucose levels as well as fatty acid breakdown.

Clinical manifestations

The symptoms of both type 1 and type 2 diabetes are similar, but they usually vary in intensity. Those associated with type 1 diabetes are more severe and faster in onset. **The symptoms are related to the osmotic effects of glucose and the abnormalities of energy partitioning.**

- Polyuria (increased urine production, particularly noticeable at night)
- Polydipsia (increased thirst).
- Fatigue due to an inability to utilise glucose and
- Marked weight loss because of the breakdown of body protein and fat as an alternative energy source to glucose.
- Blurred vision caused by a change in lens refraction
- Higher infection rate, especially Candida, and urinary tract infections due to increased urinary glucose levels.

Diagnosis

Diagnostic criteria for the type 1 and type 2 DM:

Type 2 diabetes		Type 1 diabetes
Symptomatic	Asymptomatic	
A single **fasting** plasma glucose ≥7 mmol/L OR A single **random** plasma glucose ≥11.1 mmol/L	Positive results for two of the following on 2 different days: • A **fasting** glucose ≥7 mmol/L • A random plasma glucose ≥11.1 mmol/L • HbA1c ≥48 mmol/mol OR A single random plasma glucose ≥11.1 mmol/L OR A fasting glucose ≥7 mmol/L + HbA1c ≥48 mmol/mol	Based on clinical grounds Hyperglycaemia plus two out of three of: • Short history of symptoms • Ketones • Rapid weight loss

The use of glycated haemoglobin is not appropriate for all patient groups, including those, for example, who are suspected to have type 1 diabetes, gestational diabetes, haemoglobinopathies, anaemia, acute illnesses or with renal disease. As such, current recommendations are that the diagnosis is confirmed by a glucose measurement performed in an accredited laboratory on venous serum sample. A diagnosis should never be made on the basis of glycosuria or a capillary reading of a finger-prick blood glucose alone, although such tests are commonly used for screening purposes.

I. Diabetic Emergencies

A- Hypoglycaemia

- Hypoglycaemia is the commonest side effect in the treatment of diabetes, resulting from the imbalance between glucose supply and insulin levels.
- It can occur both with insulin treatment and some oral agents, especially the longer-acting sulfonylureas.
- Biochemical hypoglycaemia for hospital in-patients is specifically defined as a blood glucose less than 4.0 mmol/L (72mg/dL).
- Most common causes of hypoglycemia involve:
  - Diet (Reduced carbohydrate intake not matched with Medication)
  - Age (More likely in older people)
  - Exercise
  - Periods of fasting (Reduced dietary intake like in Ramadan)
- Physiologically, the defence to hypoglycaemia is the release of counter-regulatory hormones adrenaline (epinephrine), noradrenaline (norepinephrine) and glucagon. This tends to occur when the venous serum glucose drops to less than 3.5 mmol/L in healthy individuals.
- **Hypoglycaemia unawareness**: is the term for when individuals do not counter-regulate to hypoglycaemia as effectively as normal.

Table 45.4 Symptoms of hypoglycaemia

Adrenergic effects/autonomic (early symptoms)[a]	Neuroglycopenic effects (late symptoms)
Sweating	Confusion
Tachycardia	Slurred speech
Palpitations	Drowsiness
Pallor	Numbness of nose, lips or fingers
Hunger	Abnormal behaviour (anxiety, agitation, aggression)
Restlessness	Visual disturbances
Trembling	Loss of consciousness, seizures, coma and death

Treatment of hypoglycaemia

- **Mild hypoglycaemia** can be managed by the individuals themselves. If the patient is able to swallow safely without the risk of aspiration, then glucose should be taken orally, as 15–20 g of fast-acting (absorbed) carbohydrate (5 glucose tablets, glass of Lucozade).
- **Severe hypoglycaemia**, if the patient is unable to swallow or if there is a risk of aspiration because of a decreased level of consciousness, parenteral treatment should be given, either as intravenous glucose or intramuscular glucagon.

B. Diabetic ketoacidosis

- Diabetic ketoacidosis (DKA) is a complex disordered metabolic state with three characteristic features: **hyperglycaemia, metabolic acidosis and ketonaemia.**
- It is most often seen in patients with **type 1 diabetes**, as a consequence of severe insulin deficiency, an increase in counter-regulatory hormones and the normal restraining effect of insulin on lipolysis being removed.
- Non-esterified fatty acids are released into the circulation and taken up by the liver, which produces acetyl coenzyme A (acetyl CoA). **Ketone bodies**, acetone, acetoacetate and hydroxybutyrate are formed and released into the circulation.
- Further, osmotic diuresis, caused by hyperglycaemia, lowers serum volume, causing **hypotension** and weakness, which is exacerbated by urinary excretion of potassium.
- **Vomiting** is attributable to stimulation of the vomiting center by ketones and catabolism of muscle protein, producing further dehydration and electrolyte disturbances.
- As serum osmolality rises, **impaired consciousness** ensues, with coma developing in approximately 10% of cases.
- **Metabolic acidosis** causes stimulation of the medullary respiratory center, giving rise to **Kussmaul respiration** (deep and rapid breathing) in a futile attempt to correct the acidosis.
- The patient's breath may have the **fruity odour** of acetone (ketones) commonly described as smelling like pear drops or nail varnish remover.
- Precipitating factors for DKA are usually omission of insulin dose, acute infection, trauma, a new diagnosis or myocardial infarction. Although diabetic ketoacidosis is normally associated with type 1 diabetes, it may rarely occur in people with type 2.

Diagnosis of diabetic ketoacidosis

The biochemical diagnosis of ketoacidosis is usually made when there is:

1. Hyperglycaemia, a blood glucose level of more than 11 mmol/L
2. Metabolic acidosis, venous pH less than 7.3 and/or bicarbonate less than 15 mmol/L
3. The presence of ketones, capillary ketones > 3 mmol/L or urinary ketones ++ or more.

Treatment of diabetic ketoacidosis

1. The first intervention is **fluid replacement**, initially with 0.9% sodium chloride, because this aids restoration of the circulatory volume, clearance of ketones and correction of electrolyte imbalances.
2. The next step is commencing **insulin therapy**, usually as a fixed-rate intravenous infusion calculated (0.1 units/kg/h). This suppresses ketoneogenesis, reduces blood glucose and corrects electrolyte imbalances.
3. Careful attention to **serum potassium levels** is required because patients may present with hyperkalaemia, but initial treatment with saline and insulin will lower levels (because total body stores of potassium are usually low). Cardiac arrhythmias can be fatal due to either hyper- or hypokalaemia.
4. **Venous thromboembolism prophylaxis** should also be given.

C. Hyperosmolar hyperglycaemic state (HHS)

- Is a serious and distinct condition associated with type 2 disease and is associated with a significant mortality rate (15–20%),
- No significant ketone production and therefore no severe acidosis.
- Hyperglycemia and osmotic diuresis leads to sever dehydration and subsequently hyperosmolarity, which lead to increase blood viscosity and the risk of thromboembolism.
- Factors precipitating HHS are infection, myocardial infarction, poor adherence with medication regimens or medicines which cause diuresis or impair glucose tolerance, for example, glucocorticoids.

Diagnosis of HHS

1. Hyperglycaemia (often in the region of 600mg/dL),
2. Severe dehydration (fluid deficit 100–220 mL/kg) and
3. Hyperosmolality.
4. There may be a mild metabolic acidosis but without marked ketone production.
5. Consciousness levels on presentation range from slight confusion to coma.

Treatment of HHS

1. Fluid replacement (Sodium chloride 0.9%) to stabilize blood pressure and improve circulation and urine output.
2. Potassium may be added if required.
3. A fixed-rate insulin infusion (0.05 units/kg/h). (Aggressive insulin administration is not required because fluid replacement also lowers serum glucose levels).
4. Prophylaxis or treatment for thromboembolism is also required.

II. Long-term diabetes complications

Diabetic complications are frequently divided into **macrovascular and microvascular** complications. The general aetiology results from atherosclerosis of blood vessels, which may lead to occlusion. The main aims of treatment are to prevent the immediate symptoms associated with diabetes and to prevent or reduce the development of the long-term disease-related complications.

A. Macrovascular disease

Cardiovascular disease

- Include **cardiovascular disease** (coronary heart disease and stroke) and **peripheral vascular disease** (PVD).
- The most common cause of death in people with type 2 diabetes
- Silent myocardial infarction (infarction with no symptoms) is more common in those with diabetes.
- Cerebrovascular disease is also more commonly associated with diabetes.

- Hypertension is twice as common amongst the diabetic population. It affects over 80% of those with type 2 diabetes.

Peripheral vascular disease (PVD)

- PVD affects the blood vessels outside the heart, it often affects the arteries of the legs.
- A cramping pain experienced on walking, due to reversible muscle ischaemia secondary to atherosclerosis.

B. Microvascular disease

Retinopathy

- The main problem with retinopathy is that it is symptomless until the disease is far advanced.
- Tight glycaemic control has been shown to prevent and delay the progression of retinopathy in patients with DM.

Nephropathy

- In diabetic renal disease, the kidneys become enlarged and the glomerular filtration rate (GFR) initially increases. However, as nephropathy progresses, the GFR starts to decline.
- However, as nephropathy progresses, the GFR starts to decline.
- The presence of nephropathy is indicated by the detection of microalbuminuria (small amounts of albumin present in urine). If higher amounts of albumin are detected, this is termed proteinuria or macroalbuminuria and signifies more severe renal damage.
- Albumin in the urine increases the risk of cardiovascular disease.
- Tight control of both glycaemic levels and blood pressure reduces the risk of developing nephropathy. The treatments of choice are (ACEI) and/or (ARBs), they provide renal protective effects.

Peripheral neuropathy

- Peripheral neuropathy is the progressive loss of functional peripheral nerve fibres.
- Diabetic neuropathies can lead to a wide variety of sensory, motor and autonomic symptoms.
- The most common is the symmetrical distal sensory type, which is particularly evident in the feet and may slowly progress to a complete loss of feeling.
- Distal motor neuropathy can lead to symptoms of impaired fine coordination of the hands and/ or foot slapping.
- Autonomic neuropathy may affect any part of the sympathetic or parasympathetic nervous systems. The most common manifestation is erectile dysfunction, bladder dysfunction and diabetic diarrhea.

III. Macro- and microvascular disease combined

Diabetic foot problems

- Foot problems often develop as a result of a combination of **sensory** and **autonomic** neuropathy, **PVD**, poor foot care and **hyperglycaemia**. Development of foot ulcers may be partly preventable by patient education.
- There are three main types of foot ulcers: **neuropathic**, **ischaemic** and **neuroischaemic.**
- **Neuropathic ulcers** occur when peripheral neuropathy causes loss of pain sensation. The ulcers can be deep but are usually painless and are caused by trauma to the foot which is not noticed until after significant damage has occurred.
- **Ischaemic ulcers** result from PVD and poor blood supply causing a reduction in available nutrients and oxygen required for healing. **Ischaemic ulcers** may be painful and usually occur on the distal ends of the toes or the sides of the feet.
- Most ulcers have elements of both neuropathy and ischaemia and are termed **neuroischaemic**.

Charcot arthropathy: Charcot arthropathy is an uncommon foot complication caused by severe neuropathy, usually in a person with palpable foot pulses. It results in chronic, progressive destruction of joints with marked inflammation. Disorganised bone remodelling leads to fractures, altered foot shape and gross deformity. Because of the deformity which occurs, excess pressure over malpositioned bone frequently leads to ulceration unless footwear is extensively modified.

Treatment of diabetes

I. Insulin therapy in type 1 diabetes

- Insulin replacement is the mainstay of treatment for all patients with type 1 diabetes.
- A balance is required between tight glycaemic control and hypoglycaemia risk.
- Side effects: Hypoglycaemia is a common physiological complication, Thickening of subcutaneous tissues can occur at injection sites because of recurrent injection in the same area, known as lipohypertrophy. Systemic allergic reactions rarely occur

Insulin preparations

Fast-acting insulins.

Conventional fast-acting insulins are soluble insulins (also known as neutral insulins). After subcutaneous injection, soluble insulin starts to appear in the circulation within 10 minutes. The concentration rises to a peak after about 2 hours and then declines over a further 4–8 hours. This absorption curve can be contrasted with the physiological insulin concentration curve, where peak concentrations are reached 30–40 minutes after a meal and decline rapidly to 10–20% of peak levels after about 2 hours.

Intermediate-acting insulins.

Conventional intermediate acting insulins are insoluble, cloudy suspensions of insulin complexed with either protamine (also known as isophane or NPH insulin) or zinc (lente insulin). Over time, insulin dissociates from the complex, which gives the preparation its extended activity. The onset

of action is usually 1–2 hours, with the peak effect being seen at 4–8 hours. There is considerable inter-patient variation in the duration of action, but it usually requires twice-daily administration to adequately cover a 24-hour period. Protamine insulin and soluble insulin do not interact when mixed together. Therefore, ready-mixed (biphasic) preparations are available that contain both isophane and soluble insulin.

Long-acting insulins.

More recently, long-acting insulin analogues, such as insulin glargine (Lantus), detemir (Levemir) and degludec (Tresiba), have been developed using recombinant DNA technology. They have a sustained duration of action, with more predictable, lat proiles of action with no pronounced peaks and less inter- and intra-subject dosing variability.

II. Management of type 2 diabetes

- Some people are able to normalise their glycaemic control by weight loss and attention to diet (diet controlled). Nevertheless, such individuals still invariably have diabetes and are at risk of developing diabetic complications.

- There are seven classes of oral agents currently available:
  - Biguanide (metformin),
  - Sulfonylureas (glibenclamide, gliclazide, glimepiride, glipizide, tolbutamide),
  - Meglitinides (repaglinide and nateglinide),
  - Thiazolidinedione (pioglitazone),
  - α-glucosidase inhibitor (acarbose),
  - Dipeptidyl peptidase-4 inhibitors (saxagliptin, sitagliptin, linagliptin, alogliptin and vildagliptin)
  - The most recently, sodium-glucose co-tansporter-2 inhibitors (canaglilozin, dapaglilozin and empaglilozin)

1. Biguanides

Metformin stimulates tissue uptake of glucose, particularly in muscle, and is thought to reduce gastro-intestinal absorption of carbohydrate. The action of metformin does not involve stimulation of pancreatic insulin secretion, and therefore it is still a beneficial agent when β-cell function has declined. Metformin also offers the advantage that it does not cause hypoglycaemia and is not associated with weight gain. Metformin has a short duration of action, with a half-life of between 1.3 and 4.5 hours, and does not bind to serum proteins. It is not metabolised and is totally renally eliminated.

The most common adverse effects of metformin, affecting about a third of patients, result from gastrointestinal disturbances including anorexia, nausea, abdominal discomfort and diarrhoea.

2. Sulfonylureas

Sulfonylureas lower blood sugar by increasing pancreatic β-cell sensitivity to glucose, allowing more insulin to be released from storage granules for a given glucose load. Sulfonylurea therapy is also associated with increased tissue sensitivity to insulin, resulting in improved insulin action.
Adverse effects: weight gain and hypoglycaemia.

3. Meglitinides

They are characterised by a more rapid onset and shorter duration of action than sulfonylureas. Their site of action is pharmacologically distinct from that of the sulfonylureas.
Meglitinides stimulate insulin secretion by inhibiting adenosine triphosphate (ATP)–sensitive potassium channels in the membrane of the pancreatic β-cells. The release of insulin only occurs in the presence of glucose. As glucose levels drop, less insulin is secreted. Conversely, if carbohydrates are consumed and glucose levels rise, insulin secretion is enhanced.
Side effects: most commonly hypoglycaemia, weight gain, visual disturbances, abdominal pain, diarrhoea, constipation, nausea and vomiting. More rarely, hypersensitivity reactions and elevation of liver enzymes can occur.

4. Thiazolidinediones

Glitazones act as agonists of the nuclear peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ is mostly expressed in adipose tissue but is also found in pancreatic β-cells, vascular endothelium and macrophages. They also suppress gluconeogenesis in the liver and, by increasing insulin sensitivity in adipose tissue, suppress free fatty acid concentrations.
Adverse effect: Congestive cardiac failure.

5. Sodium-glucose co-tansporter-2 inhibitors

They work by lowering the renal threshold to glucose, which leads to its urinary excretion. There are currently three licenced products: canaglilozin, dapaglilozin and empaglilozin.
They selectively and reversibly inhibit the sodium-glucose co-transporter 2 (SGLT-2), which is selectively expressed in the proximal renal tubules of the kidney. By inhibiting SGLT-2 the reabsorption of glucose is reduced.
Side effects: Serious and life-threatening cases of DKA reported, infections (especially urinary tract infections, vulvovaginitis and related genital infections),

6. Dipeptidyl peptidase-4 inhibitors

The dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of drugs that work on the incretin system. They are also commonly referred to as the ‘gliptins’ – sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin.
Incretins play a role in increasing endogenous insulin in response to a high glucose load post-prandially. They also reduce the amount of glucose produced by the liver when glucose levels are sufficiently high.
Side effects: gastro-intestinal and upper respiratory tract infection. DPP-4 inhibitors do not cause hypoglycaemia. Vildagliptin has been associated with rare reports of liver dysfunction.

7. Incretin mimetics

The incretin mimetics bind to and activate the glucagon-like peptide-1 (GLP-1) receptor, hence increasing insulin secretion, suppressing glucagon secretion, increasing satiety and slowing gastric emptying. All of these effects help lower blood glucose levels.
Side effects: nausea and other gastro-intestinal disturbances

A Glucosidase Inhibitors (Acarbose)

Acarbose reduces carbohydrate digestion by interfering with gastro-intestinal glucosidase activity, reducing the post-prandial hyperglycaemic peaks. Acarbose is minimally absorbed in unchanged form from the gastro-intestinal tract.
Adverse effect is abdominal discomfort associated with flatulence and diarrhoea.

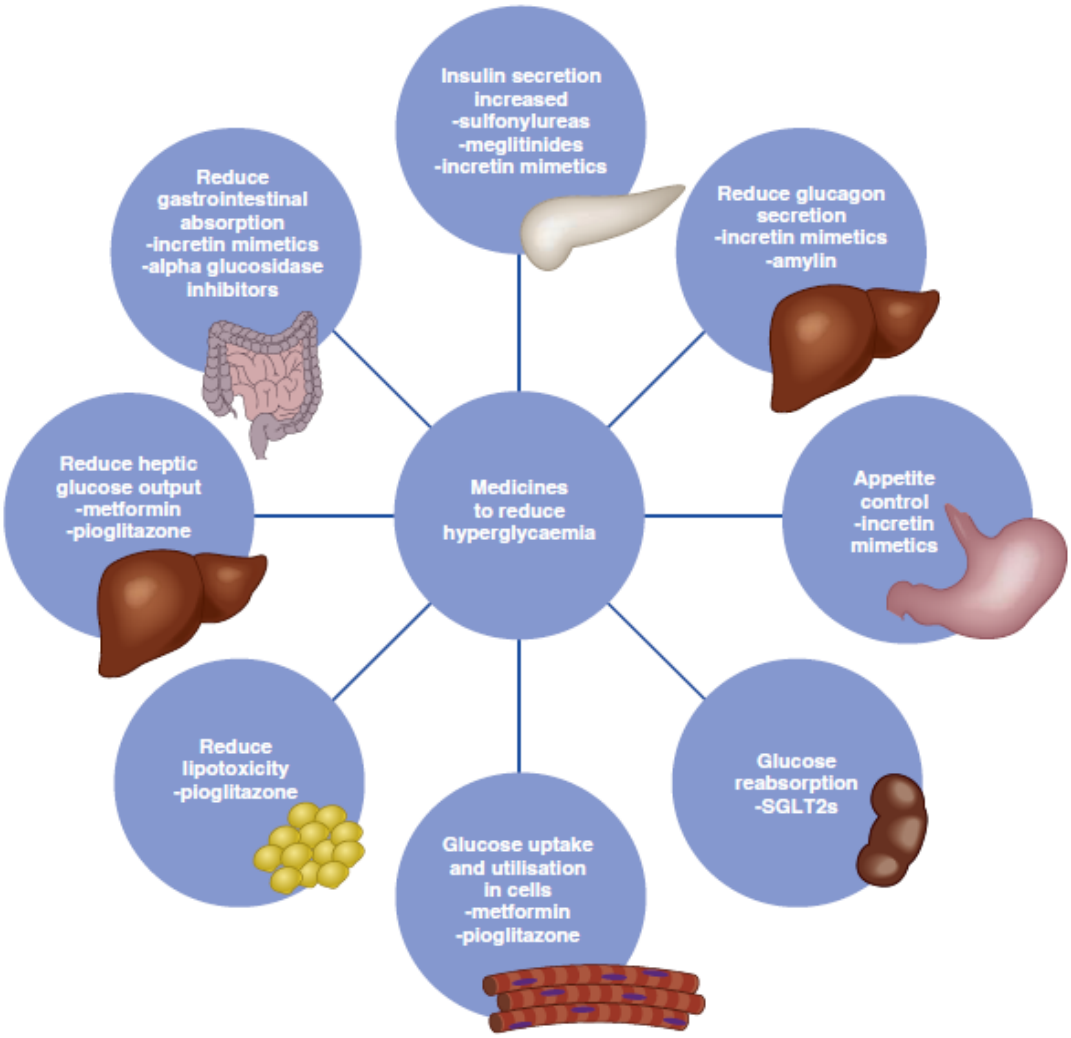

Fig. 45.3 Mode and place of action of the oral hypoglycaemic agents.

Reference:
Clinical pharmacy and therapeutics, 6th edition, 2019