

Chapter 19 | Insulin, Oral Antidiabetic Drugs and Glucagon

Diabetes mellitus (DM) It is a metabolic disorder characterized by hyperglycaemia, (fasting plasma glucose ≥ 126 mg/dL and/or ≥ 200 mg/dL 2 hours after 75 g oral glucose), glycosuria, hyperlipidaemia, negative nitrogen balance and sometimes ketonaemia. A widespread pathological change is thickening of capillary basement membrane, increase in vessel wall matrix and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy and peripheral vascular insufficiency.

Enhanced nonenzymatic glycosylation of tissue proteins due to persistent exposure to high glucose concentrations and the accumulation of larger quantities of sorbitol (a reduced product of glucose) in tissues are believed to be causative in the pathological changes of diabetes. The concentration of glycosylated haemoglobin (HbA_{1c}) is taken

as an index of protein glycosylation: it reflects the state of glycaemia over the preceding 2–3 months.

Two major types of diabetes mellitus are:

Type I Insulin-dependent diabetes mellitus (IDDM)/juvenile onset diabetes mellitus:

There is β cell destruction in pancreatic islets; majority of cases are autoimmune (type 1A) antibodies that destroy β cells are detectable in blood, but some are idiopathic (type 1B)—no β cell antibody is found. In all type 1 cases circulating insulin levels are low or very low, and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition.

Type II Noninsulin-dependent diabetes mellitus (NIDDM)/maturity onset diabetes mellitus:

There is no loss or only moderate reduction in β cell mass; insulin in circulation is low,

Approaches to drug therapy in type 2 DM

Improve insulin availability

Exogenous insulin

Sulfonylureas

Meglitinide/phenylalanine analogues

Dipeptidyl peptidase-4 inhibitors (DPP-4Is)

GLP-1 receptor agonists

Major limitations (except for DPP-4Is and GLP1 agonists)

Multiple daily injections (Insulins)

Hypoglycaemic episodes

Weight gain

Concern about premature atherosclerosis due to hyperinsulinaemia

Overcome insulin resistance

Biguanides (Metformin)

Thiazolidinediones (Pioglitazone)

α glucosidase inhibitors

Major limitations

Inability to achieve normoglycaemia by themselves in many patients, especially moderate-to-severe cases

normal or even high, no anti- β -cell antibody is demonstrable; has a high degree of genetic predisposition; generally has a late onset (past middle age). Over 90% cases of diabetes are type 2 DM. Causes may be:

- Abnormality in gluco-receptor of β cells so that they respond at higher glucose concentration or relative β cell deficiency. In either way, insulin secretion is impaired; may progress to β cell failure.
- Reduced sensitivity (relative resistance); of peripheral tissues to insulin: reduction in number of insulin receptors, i.e. 'down regulation' of insulin receptors. Many hypertensives are hyperinsulinaemic, but normoglycaemic; and have associated dyslipidaemia, hyperuricaemia, abdominal obesity (metabolic syndrome). Thus, there is relative insulin resistance, particularly at the level of liver, muscle and fat. Hyperinsulinaemia *per se* has been implicated in causing angiopathy.
- Excess of hyperglycaemic hormones (glucagon, etc.)/obesity: cause relative insulin deficiency—the β cells lag behind.

In most cases, both relative insulin resistance and β cell insufficiency are produced by a combination of genetic and environmental factors.

Other rare forms of DM are those due to specific genetic defects (type-3) like 'maturity onset diabetes of young' (MODY), other endocrine disorders, pancreatectomy and 'gestational diabetes mellitus' (GDM, type-4).

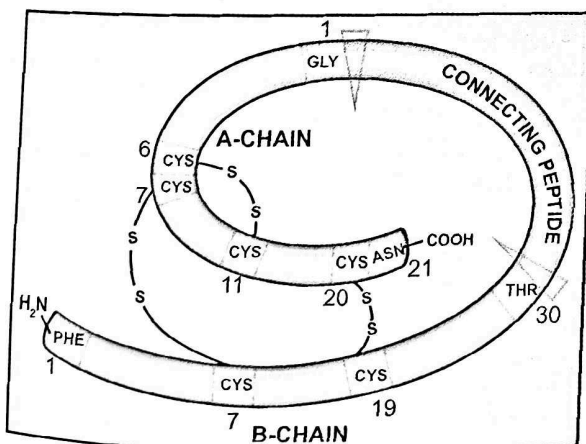


Fig. 19.1: Human proinsulin; simplified structure depicting the main features. The connecting peptide, having 35 amino acids, is split off leaving insulin molecule with two chains joined by two disulfide bridges

INSULIN

Insulin was discovered in 1921 by Banting and Best who demonstrated the hypoglycaemic action of an extract of pancreas prepared after degeneration of the exocrine part due to ligation of pancreatic duct. It was first obtained in pure crystalline form in 1926 and the chemical structure was fully worked out in 1956 by Sanger.

Insulin is a two chain polypeptide having 51 amino acids and MW about 6000. The A-chain has 21 while B-chain has 30 amino acids. There are minor differences between human, pork and beef insulins:

Species	A-chain		B-chain
	8th AA	10th AA	30th AA
Human	THR	ILEU	THR
Pork	THR	ILEU	ALA
Beef	ALA	VAL	ALA

Thus, pork insulin is more homologous to human insulin than is beef insulin. The A and B chains are held together by two disulfide bonds.

Insulin is synthesized in the β cells of pancreatic islets as a single chain peptide *Preproinsulin* (110 AA) from which 24 AAs are first removed to produce *Proinsulin* (Fig. 19.1). The connecting or 'C' peptide (35 AA) is split off by proteolysis in Golgi apparatus; both insulin and C peptide are stored in granules within the cell. The C peptide is secreted in the blood along with insulin.

Assay Insulin was bioassayed either by measuring blood sugar depression in rabbits or by its potency to induce hypoglycaemic convulsions in mice. With the availability of pure preparations, insulin is now assayed chemically and the quantity expressed by weight (1 mg of International standard of insulin = 28 Units). Plasma insulin can be measured by radioimmunoassay or enzyme immunoassay.

Regulation of insulin secretion

Under basal condition ~1U insulin is secreted per hour by human pancreas. Much larger quantity is secreted after every meal. Secretion of insulin from β cells is regulated by chemical, hormonal and neural mechanisms.

Chemical The β cells have a glucose sensing mechanism dependent on entry of glucose into

the β cells (through the aegis of a glucose transporter GLUT1) and its phosphorylation by glucokinase. Glucose entry and metabolism leads to activation of the glucosensor and production of ATP which inhibits the ATP-sensitive K^+ channel (K_{ATP}^+) resulting in partial depolarization of the β cells (see Fig. 19.6). This increases intracellular Ca^{2+} availability (due to increased influx, decreased efflux and release from intracellular stores) $\rightarrow$ exocytotic release of insulin storing granules. Other nutrients that can evoke insulin release are—amino acids, fatty acids and ketone bodies, but glucose is the principal regulator and it stimulates the synthesis of insulin as well. Glucose induces a brief pulse of insulin output within 2 min (first phase) followed by a delayed but more sustained second phase of insulin release.

Glucose and other nutrients are 2–4 times more effective in invoking insulin release when given orally than i.v. They generate chemical signals 'incretins' from the gut which act on β cells in the pancreas to cause anticipatory release of insulin. The incretins involved are glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), vasoactive intestinal peptide (VIP), pancreatic polypeptide (PP), etc.; but various incretins may mediate signal from different nutrients. Glucagon and some of these peptides enhance insulin release by increasing cAMP formation in the β cells.

Hormonal A number of hormones, e.g. growth hormone, corticosteroids, thyroxine modify insulin release in response to glucose. More important are the intra-islet paracrine interactions between the hormones produced by different types of islet cells. The β cells constitute the core of the islets and are the most abundant cell type. The α cells, comprising 25% of the islet cell mass, surround the core and secrete glucagon. The δ cells (5–10%) elaborating somatostatin are interspersed between the α cells. There are some PP (pancreatic polypeptide containing) cells as well.

- Somatostatin inhibits release of both insulin and glucagon.

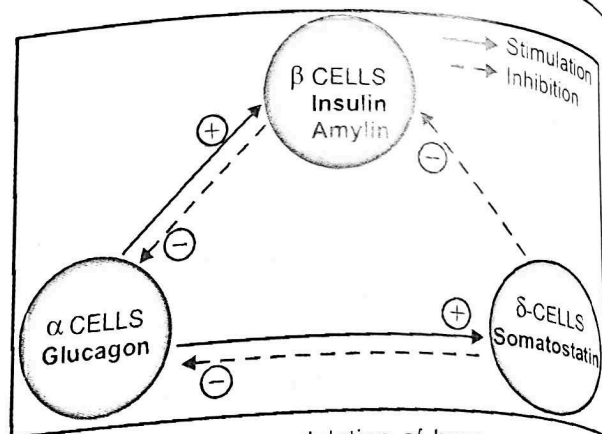


Fig. 19.2: Paracrine modulation of hormone secretion within the pancreatic islets of Langerhans

- Glucagon evokes release of insulin as well as somatostatin.
- Insulin inhibits glucagon secretion. Amylin, another β cell polypeptide released with insulin, inhibits glucagon secretion through a central site of action in the brain.

The three hormones released from closely situated cells influence each other's secretion and appear to provide fine tuning of their output in response to metabolic needs (Fig. 19.2).

Neural The islets are richly supplied by sympathetic and vagal nerves.

- Adrenergic α_2 receptor activation decreases insulin release (predominant) by inhibiting β cell adenylyl cyclase.
- Adrenergic β_2 stimulation increases insulin release (less prominent) by stimulating β cell adenylyl cyclase.
- Cholinergic—muscarinic activation by ACh or vagal stimulation causes insulin secretion through IP_3 /DAG-increased intracellular Ca^{2+} in the β cells.

However, neural influences have only modulatory effect on insulin secretion.

ACTIONS OF INSULIN

The overall effects of insulin are to dispose meal derived glucose, amino acids, fatty acids and favour storage of fuel. It is a major anabolic hormone: promotes synthesis of glycogen, lipids and protein. The actions of insulin and the results of its deficiency can be summarized as:

1. *Insulin facilitates glucose transport across cell membrane:* skeletal muscle and fat are highly sensitive. The availability of glucose intracellularly is the limiting factor for its utilization. However, glucose entry in liver, brain, RBC, WBC and renal medullary cells is largely independent of insulin. Ketoacidosis interferes with glucose utilization by brain and contributes to diabetic coma. Muscular activity induces glucose entry in muscle cells without the need for insulin. As such, exercise has insulin sparing effect.

The intracellular pool of vesicles containing glucose transporter glycoproteins GLUT4 (insulin activated) and GLUT1 is in dynamic equilibrium with the GLUT vesicles inserted into the membrane. This equilibrium is regulated by insulin to favour translocation to the membrane. Moreover, on a long-term basis, synthesis of GLUT4 is upregulated by insulin.

2. The first step in intracellular utilization of glucose is its phosphorylation to form glucose-6-phosphate. This is enhanced by insulin through *increased production of glucokinase*. Insulin facilitates glycogen synthesis from glucose in liver, muscle and fat by stimulating the enzyme glycogen synthase. It also inhibits glycogen degrading enzyme phosphorylase → decreased glycogenolysis in liver.

3. *Insulin inhibits gluconeogenesis* (from protein, FFA and glycerol) in liver by gene mediated decreased synthesis of phosphoenol pyruvate carboxykinase. In insulin deficiency, proteins and amino acids are funneled from peripheral tissues

to liver where these substances are converted to carbohydrate and urea. Thus, in diabetes there is underutilization and over production of glucose leading to hyperglycaemia and glycosuria.

4. *Insulin inhibits lipolysis* in adipose tissue and favours triglyceride synthesis. In diabetes increased amount of fat is broken down due to unchecked action of lipolytic hormones (glucagon, Adr, thyroxine, etc.) → increased FFA and glycerol in blood → taken up by liver to produce acetyl-CoA. Normally acetyl-CoA is resynthesized to fatty acids and triglycerides, but this process is reduced in diabetics and acetyl CoA is diverted to produce ketone bodies (acetone, acetoacetate, β -hydroxy-butyrate). The ketone bodies are released in blood and partly used up by muscle and heart as energy source, but when their capacity is exceeded, ketonaemia and ketonuria result.

5. Insulin enhances transcription of vascular endothelial lipoprotein lipase, thereby accelerating clearance of VLDL and chylomicrons.

6. Insulin facilitates AA entry into muscles and most other cells. Their synthesis into proteins is enhanced, and protein breakdown is inhibited. Insulin deficiency leads to protein breakdown → AAs are released in blood → taken up by liver and converted to pyruvate, glucose and urea. The excess urea produced is excreted in urine resulting in negative nitrogen balance. Thus, catabolism takes the upper hand over anabolism in the diabetic state.

Most of the above metabolic actions of insulin are exerted within seconds or minutes and are

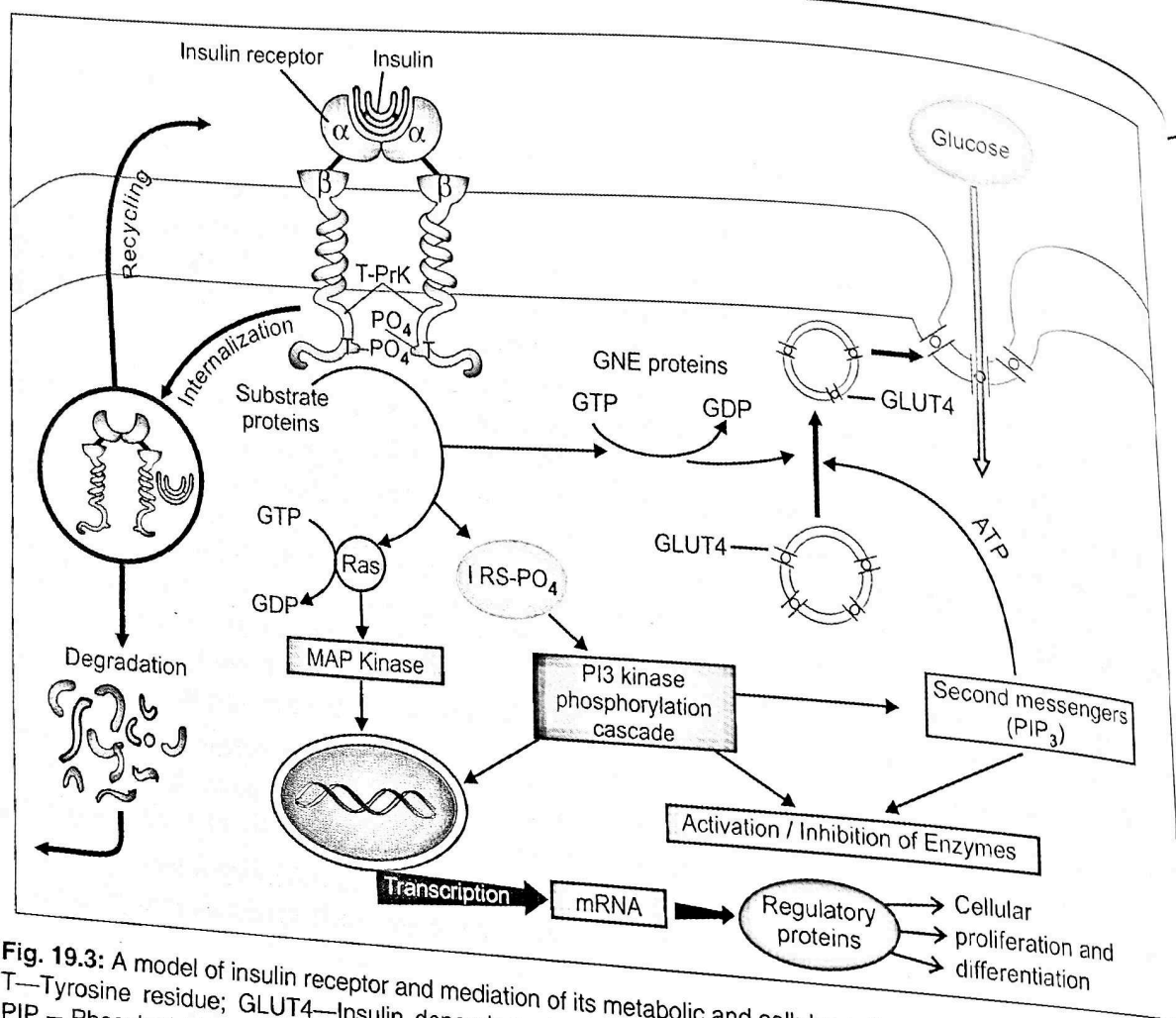


Fig. 19.3: A model of insulin receptor and mediation of its metabolic and cellular actions
 T—Tyrosine residue; GLUT4—Insulin dependent glucose transporter; IRS—Insulin receptor substrate proteins;
 PIP₃—Phosphatidyl inositol trisphosphate; PI₃ kinase—Phosphatidylinositol-3 kinase; GNE proteins—Guanine nucleotide exchange proteins; MAP kinase—Mitogen-activated protein kinase; T-PrK—Tyrosine protein kinase; Ras—Regulator of cell division and differentiation (protooncogene product).

called the *rapid actions*. Others involving DNA mediated synthesis of glucose transporter and some enzymes of amino acid metabolism have a latency of few hours—the *intermediate actions*. In addition insulin exerts major *long-term* effects on multiplication and differentiation of many types of cells.

Mechanism of action Insulin acts on specific receptors located on the cell membrane of practically every cell, but their density depends on the cell type: liver and fat cells are very rich. The insulin receptor is a receptor tyrosine kinase (RTK) which is a heterotetrameric glycoprotein consisting of 2 extracellular α and 2 transmembrane β subunits linked together by disulfide bonds. It is oriented across the cell membrane as a heterodimer (Fig. 19.3). The α subunits carry insulin binding sites, while the β subunits have tyrosine protein kinase activity.

Binding of insulin to α subunits induces aggregation and internalization of the receptor along with the bound insulin molecules. This activates tyrosine kinase activity of the β subunits $\rightarrow$ pairs of β subunits phosphorylate tyrosine residues on each other $\rightarrow$ expose the catalytic site to phosphorylate tyrosine residues of Insulin Receptor Substrate proteins (IRS1, IRS2, etc) and other caveolar/noncaveolar proteins. In turn, a cascade of phosphorylation and dephosphorylation reactions involving phosphatidylinositol 3 kinase (PI3 kinase) and other kinases is set into motion which amplifies the signal and results in stimulation or inhibition of enzymes involved in the rapid metabolic actions of insulin.

Second messengers like phosphatidyl inositol trisphosphate (PIP₃) which are generated through activation of a specific PI3-kinase also mediate the action of insulin on metabolic enzymes.

Insulin stimulates glucose transport across cell membrane by ATP dependent translocation of glucose transporter

GLUT4 to the plasma membrane. The second messenger PIP₂ and certain tyrosine phosphorylated guanine nucleotide exchange proteins play crucial roles in the insulin sensitive translocation of GLUT4 from cytosol to the plasma membrane, especially in skeletal muscle and adipose tissue. Over a period of time insulin also promotes expression of the genes directing synthesis of GLUT4. Genes for a large number of enzymes and carriers are regulated by insulin through Ras/Raf and MAP-Kinase as well as through the phosphorylation cascade. Long-term effects of insulin are exerted by generation of transcription factors promoting proliferation and differentiation of specific cells.

The internalized receptor-insulin complex is either degraded intracellularly or returned back to the surface from where the insulin is released extracellularly. The relative preponderance of these two processes differs among different tissues: maximum degradation occurs in liver, least in vascular endothelium.

Fate of insulin Insulin is distributed only extracellularly. It is a peptide, and gets degraded in the g.i.t. if given orally. Injected insulin or that released from pancreas is metabolized primarily in liver and to a smaller extent in kidney and muscles. Nearly half of the insulin entering portal vein from pancreas is inactivated in the first passage through liver. Thus, normally liver is exposed to a much higher concentration (4–8 fold) of insulin than are

other tissues. As noted above, degradation of insulin after receptor mediated internalization occurs to variable extents in most target cells. During biotransformation the disulfide bonds are reduced—A and B chains are separated. These are further broken down to the constituent amino acids. The plasma $t_{1/2}$ of insulin is 5–9 min.

Preparations of insulin

The older commercial insulin preparations were produced from beef and pork pancreas. They contained ~1% (10,000 ppm) of other proteins (proinsulin, other polypeptides, pancreatic proteins, insulin derivatives, etc.) which were potentially antigenic. Such insulins are no longer produced and have been totally replaced by highly purified pork/beef insulins, recombinant human insulins and insulin analogues.

Highly purified insulin preparations

In the 1970s improved purification techniques like gel filtration and ion-exchange chromatography were applied to produce 'single peak' and 'monocomponent (MC)' insulins which contain <10 ppm proinsulin. The MC insulins are more stable and cause less insulin resistance or injection site lipodystrophy. The immunogenicity of pork MC insulin is similar to that of recombinant human insulin.

Types of insulin preparations

Regular (soluble) insulin It is a buffered neutral pH solution of unmodified insulin stabilized by a small amount of zinc. At the concentration of the injectable solution, the insulin molecules self aggregate to form hexamers around the zinc ions. After s.c. injection, insulin monomers are released gradually by dilution, so that absorption occurs slowly. Peak action is produced only after 2–3 hours and action continues upto 6–8 hours. The absorption pattern is also affected by dose; higher doses act longer. When injected s.c. just before a meal, this pattern often creates a mismatch between the need and the availability of insulin to result in early postprandial hyperglycaemia and late postprandial hypoglycaemia. Regular insulin is optimally injected 1 hour before a meal. Regular insulin injected s.c. is also not suitable for providing a low constant basal level of action in the interdigestive period. However, the slow onset of action is not applicable to i.v. injection, because the insulin hexamer dissociates rapidly to produce prompt action. Regular insulin is the only insulin used for i.v. injection.

To overcome the above problems, some long-acting 'modified' or 'retard' preparations of insulin were soon developed. Recently, both rapidly acting as well as peakless and long-acting insulin analogues have become available.

For obtaining retard preparations, insulin is rendered insoluble either by complexing it with protamine (a small molecular basic protein) or by precipitating it with excess zinc and increasing the particle size.

Lente insulin (Insulin-zinc suspension): Two types of insulin-zinc suspensions have been produced. The one with large particles is crystalline and practically insoluble in water (ultralente). It is long-acting. The other has smaller particles and is amorphous (semilente), is short-acting. Their 7:3 ratio mixture is called 'Lente insulin' and is intermediate-acting.

Isophane (Neutral Protamine Hagedorn or NPH) insulin: Protamine is added in a quantity

just sufficient to complex all insulin molecules; neither insulin nor protamine is present in free form and pH is neutral. On s.c. injection, the complex dissociates slowly to yield an intermediate duration of action. However, the time course of absorption and intensity of action of NPH insulin is relatively inconsistent. It is mostly combined with regular insulin (70:30 or 50:50) and injected s.c. twice daily before breakfast and before dinner (split-mixed regimen).

1. Highly purified (monocomponent) pork regular insulin: ACTRAPID MC, RAPIDICA 40 U/ml inj.
2. Highly purified (MC) pork lente insulin: LENTARD, MONOTARD MC, LENTINSULIN-HPI, ZINULIN 40 U/ml
3. Highly purified (MC) pork isophane (NPH) insulin: INSULATARD 40 U/ml inj.
4. Mixture of highly purified pork regular insulin (30%) and isophane insulin (70%): RAPIMIX, MIXTARD 40 U/ml inj.

Human insulins In the 1980s, the human insulins (having the same amino acid sequence as human insulin) were produced by recombinant DNA technology in *Escherichia coli*—'proinsulin recombinant bacterial' (prb) and in yeast—'precursor yeast recombinant' (pyr), or by 'enzymatic modification of porcine insulin' (emp).

1. HUMAN ACTRAPID: Human *regular* insulin; 40 U/ml, 100 U/ml, ACTRAPID HM PENFIL 100 U/ml pen inj., WOSULIN-R 40 U/ml inj vial and 100 U/ml pen injector cartridge.
2. HUMAN MONOTARD, HUMINSULIN-L: Human *lente* insulin; 40 U/ml, 100 U/ml.
3. HUMAN INSULATARD, HUMINSULIN-N: Human *isophane* insulin 40 U/ml. WOSULIN-N 40 U/ml inj. vial and 100 U/ml pen injector cartridge.
4. HUMAN ACTRAPANE, HUMINSULIN 30/70, HUMAN MIXTARD: Human *soluble* insulin (30%) and *isophane* insulin (70%), 40 U/ml. and 100 U/ml vials. WOSULIN 30/70: 40 U/ml vial and 100 U/ml cartridge.
5. ACTRAPANE HM PENFIL: Human *soluble* insulin 30% + *isophane* insulin 70% 100 U/ml pen injector.
6. INSUMAN 50/50: Human *soluble* insulin 50% + *isophane* insulin 50% 40 U/ml inj; HUMINSULIN 50/50, HUMAN MIXTARD 50; WOSULIN 50/50 40 U/ml vial, 100 U/ml cartridge.

In the USA pork and beef insulins are no longer manufactured, but they are still available in U.K., India and some European countries. In Britain now > 90% diabetics who use insulin

are taking human insulins or insulin analogues. In India also human insulins and analogues are commonly used, except for considerations of cost. Human insulin is more water soluble as well as hydrophobic than porcine or bovine insulin. It has a slightly more rapid s.c. absorption, earlier and more defined peak concentration and slightly shorter duration of action. Human insulin is also modified similarly to produce isophane (NPH) and lente preparations. Lente human insulin is no longer prepared in the USA.

The allegation that human insulin produces more *hypoglycaemic unawareness* has not been substantiated. However, after prolonged treatment, irrespective of the type of insulin used, many diabetics develop relative hypoglycaemic unawareness/change in hypoglycaemic symptoms, because of autonomic neuropathy, changes in perception/attitude and other factors.

Clinical superiority of human insulin over pork MC insulin has not been demonstrated. Though new patients may be started on human insulins, the only indication for transfer from purified pork to human insulin is allergy to pork insulin. It is unwise to transfer stabilized patients from one to another species insulin without good reason.

Insulin analogues

Using recombinant DNA technology, analogues of insulin have been produced which have modified pharmacokinetics on s.c. injection, but similar pharmacodynamic effects and immunogenicity. Greater stability and consistency of the preparations are the other advantages.

Insulin lispro: Produced by reversing proline and lysine at the carboxy terminus B 28 and B 29 positions, it forms very weak hexamers that dissociate rapidly after s.c. injection resulting in a quick and more defined peak as well as shorter duration of action. Individual variability in absorption is minimized. Unlike regular insulin, it is best injected s.c. 0–20 min before a meal. A better control of meal-time glycaemia and a lower incidence of late post-prandial hypoglycaemia have been obtained. Using a regimen of 2–3 daily meal-time insulin lispro injections, a slightly greater reduction in HbA_{1c} compared to regular insulin has been reported. Fewer hypoglycaemic episodes occurred. HUMALOG 100 U/ml, 3 ml cartridge, 10 ml vial.

Insulin aspart: The proline at B 28 of human insulin is replaced by aspartic acid. This change reduces the tendency for self-aggregation, and a time-action profile similar to insulin lispro is obtained. It more closely mimics the physiological insulin release pattern after a meal, with the same advantages as above.

NOVOLOG, NOVORAPID 100 U/ml inj.

Biphasic insulin aspart: The 70:30 mixture of isophane complex of insulin aspart with uncomplexed insulin aspart has the advantage of rapid and predictable onset along with intermediate duration of action. It is called 'biphasic insulin aspart', and can be injected twice daily just before each major meal.

NOVOMIX 30 FLEXPEN 100 U/mL in 3 mL inj., also as PENFIL injection.

Insulin glulisine: Another rapidly acting insulin analogue with lysine replacing asparagine at B 23 and glutamic acid replacing lysine at B 29. Properties and advantages are similar to insulin lispro. It has been particularly used for continuous subcutaneous insulin infusion (CSII) by a pump.

Insulin glargine: This long-acting biosynthetic insulin has 2 additional arginine residues at the carboxy terminus of B chain and glycine replaces asparagine at A 21. This analogue remains soluble at pH 4 of the formulation, but precipitates at neutral pH encountered on s.c. injection. A depot is created from which monomeric insulin dissociates slowly to enter the circulation. Onset of action is delayed, but relatively low blood levels of insulin are maintained for upto 24 hours. A smooth 'peakless' effect is obtained. Thus, it is suitable for once daily injection to provide background insulin action. Fasting and interdigestive blood glucose levels are effectively lowered irrespective of time of the day when injected or the site of s.c. injection. It is mostly injected at bed time. Lower incidence of night-time hypoglycaemic episodes compared to isophane insulin has been reported. However, it does not control meal-time glycaemia, for which a rapid acting insulin or an oral hypoglycaemic is used concurrently. Because of acidic pH, it cannot be mixed with any other insulin preparation; must be injected separately.

LANTUS OPTISET 100 U/ml in 5 ml vial and 3 ml prefilled pen injector.

Insulin detemir Myristoyl (a fatty acid) radical is attached to the amino group of lysine at B29 of insulin chain. As a result, it binds to albumin after s.c. injection from which the free form becomes available slowly. A pattern of insulin action almost similar to that of insulin glargine is obtained, but twice daily dosing may be needed. LEVEMIR FLEXPEN 100 U/mL in 3 mL prefilled pen injector.

Insulin degludec It is a new ultra long-acting insulin analogue with a flat plasma glucose lowering effect lasting for ~ 40 hours, suitable for meeting *basal insulin requirement* in type 1 and type 2 diabetic patients. After single daily injection the day-to-day variability in response and risk of nocturnal hypoglycaemia are less than with insulin glargine. An alternate day regimen has also been tried, but may not be satisfactory. It has also been coformulated with rapid-acting insulin aspart.

REACTIONS TO INSULIN

1. Hypoglycaemia This is the most frequent and potentially the most serious reaction. Hypoglycaemic episodes are more common in patients of 'labile' diabetes in whom insulin requirement fluctuates unpredictably. Hypoglycaemia can occur in any diabetic following inadvertent injection of large dose, by missing a meal after injection or by performing vigorous exercise. The symptoms can be divided into those due to counter-regulatory sympathetic stimulation, viz. sweating, anxiety, palpitation, tremor; and those due to deprivation of the brain of its essential nutrient glucose (neuroglucopenic symptoms)—dizziness, headache, behavioural changes, visual disturbances, hunger, fatigue, weakness, muscular incoordination and sometimes fall in BP. Generally, the reflex sympathetic symptoms occur, before the neuroglucopenic, but the warning symptoms of hypoglycaemia differ from patient to patient and also depend on the rate of fall in blood glucose level. Diabetic neuropathy can abolish the autonomic symptoms. *Hypoglycaemic unawareness* (loss of warning symptoms) tends to develop in patients who experience frequent episodes of hypoglycaemia.

Finally, when blood glucose falls further (to < 40 mg/dl) mental confusion, abnormal behaviour, seizures and coma occur. Irreversible neurological deficits are the sequelae of prolonged hypoglycaemia.

Treatment Glucose (or glucose yielding carbohydrate, e.g. sugar) 15–20 g orally reverses the symptoms rapidly in most cases. If no improvement occurs, the same amount may be repeated after 15–20 min. In severe cases 30–50 mL of 50% glucose may be injected i.v. over 10 min. Glucagon 0.5–1 mg i.v. or Adr 0.2 mg s.c. (less desirable) may be given as an expedient measure in patients who are not able to take sugar orally and injectable glucose is not available.

2. Local reactions Swelling, erythema and stinging sometimes occur at the injected site, especially in the beginning. *Lipodystrophy* of the subcutaneous fat around the injection site occurred occasionally with the older pork/beef insulin preparations. This is rare with the newer preparations.

3. Allergy This is due to contaminating proteins, and is very rare with human/highly purified insulins.

Urticaria, angioedema and anaphylaxis are the manifestations.

4. Edema Some patients develop short-lived dependent edema (due to Na^+ retention) when insulin therapy is started.

Drug interactions

1. β adrenergic blockers prolong hypoglycaemia by inhibiting compensatory mechanisms operating through β_2 receptors (β_1 selective blockers are less liable). Warning signs of hypoglycaemia like palpitation, tremor and anxiety are masked.
2. Thiazides, furosemide, corticosteroids, oral contraceptives, salbutamol, nifedipine tend to raise blood sugar and reduce effectiveness of insulin.
3. Acute ingestion of alcohol can precipitate hypoglycaemia by depleting hepatic glycogen.
4. Lithium, high dose aspirin and theophylline may also accentuate hypoglycaemia by enhancing insulin secretion, as well as peripheral glucose utilization.

USES OF INSULIN

Diabetes mellitus The purpose of therapy in diabetes mellitus is to restore metabolism to normal, avoid symptoms due to hyperglycaemia and glucosuria, prevent short-term complications (infection, ketoacidosis, etc.) and long-term sequelae (cardiovascular, retinal, neurological, renal, etc.).

The generally accepted criteria for adequate glycaemia control in an adult diabetic treated with insulin or oral antidiabetics are:

- Fasting (morning) blood glucose levels 90–130 mg/dl
- Blood glucose levels ≤ 150 mg/dl 2 hours after meals
- HbA_{1c} levels < 7%.

Insulin is effective in all forms of diabetes mellitus and is a must for type 1 cases, as well as for post pancreatectomy diabetes and gestational diabetes. Many type 2 cases can be controlled by lifestyle measures like diet, reduction in body weight and appropriate exercise supplemented, if required, by oral antidiabetics. Insulin is needed by such patients when:

- Not controlled by diet and exercise or when these are not practicable.
- Primary or secondary failure of oral antidiabetics or when these drugs are not tolerated.
- Under weight patients.
- Temporarily to tide over infections, trauma, surgery, pregnancy. In the perioperative period and during labour, monitored i.v. insulin infusion is preferable.
- Any complication of diabetes, e.g. keto-acidosis, nonketotic hyperosmolar coma, gangrene of extremities.

When instituted, insulin therapy has to be tailored according to the requirement and convenience of each patient. A tentative regimen is instituted and the insulin requirement is assessed by testing blood glucose levels (portable glucometers are available). Most type 1 patients require 0.4–0.8 U/kg/day. In type 2 patients, insulin dose varies (0.2–1.6 U/kg/day) with the severity of diabetes and body weight: obese patients require higher per kg doses due to relative insulin resistance.

Any satisfactory insulin regimen should provide basal control by inhibiting hepatic glucose output, lipolysis and protein breakdown, as well as supply extra amount to meet postprandial needs for disposal of absorbed glucose and amino acids. A single daily injection of any long-acting or intermediate-acting or short-acting insulin or a mixture of these cannot fulfil both

these requirements. Either multiple (2–4) injections daily of long and short acting insulins or a single injection daily of long-acting insulin supplemented by oral hypoglycaemics for meal time glycaemia is used.

Split-mixed regimen: A frequently selected regimen utilizes mixture of regular with lente or isophane insulin. The total daily dose of a 30:70 or 50:50 mixture of regular and NPH insulin is usually split into two and injected s.c. before breakfast and before dinner. Several variables, viz. site and depth of s.c. injection, posture, regional muscular activity, injected volume and type of insulin alter the rate of absorption of s.c. injected insulin, so that variability in time-course of insulin action within the same patient is large. The advantage is that only two daily injections are required, but the post-lunch glycaemia may not be adequately covered (see Fig. 19.4 A), and late postprandial hypoglycaemia may occur.

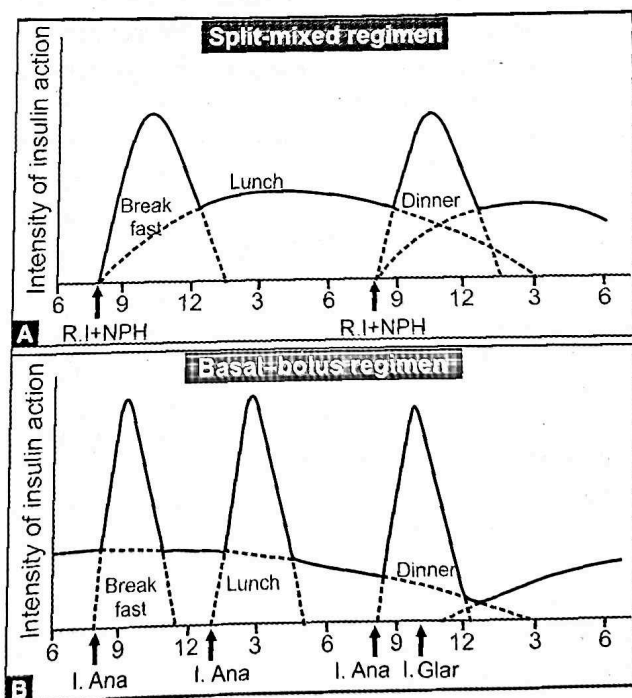


Fig. 19.4: Diagrammatic depiction of pattern of insulin action obtained with two commonly employed insulin regimens

Arrow indicates subcutaneous insulin injection.

I. Ana—Insulin analogue (rapid acting); I. Glar—Insulin glargine; R.I.—Regular insulin; NPH—Neutral protamine Hagedorn (isophane) insulin

Basal-bolus regimen: This is a more intensive regimen that is now advised. It needs 3–4 daily injections (see Fig. 19.4B). A long-acting insulin (glargine) is injected once daily either before breakfast or before bed-time for basal coverage along with 2–3 meal-time injections of a rapid acting preparation (insulin lispro or aspart). The dose of basal insulin is usually kept constant for a patient, while that of meal time rapid acting insulin is varied according to carbohydrate content of food consumed. Such intensive regimens more completely meet the objective of achieving round-the-clock euglycaemia, but are more demanding and expensive.

The large multicentric Diabetes Control and Complications Trial (DCCT) among type 1 patients has established that intensive insulin therapy markedly reduces the occurrence of primary diabetic retinopathy, neuropathy, nephropathy and slows progression of these complications in those who already have them, in comparison to conventional regimens which attain only intermittent euglycaemia. Thus, the risk of microvascular disease appears to be related to the glycaemia

control. The 'UK Prospective Diabetes Study' (UK PDS, 1998) has extended these observations to type 2 DM patients as well. Since the basis of pathological changes in both type 1 and type 2 DM is accumulation of glycosylated proteins and sorbitol in tissues as a result of exposure to high glucose concentrations, tight glycaemia control can delay end-organ damage in all diabetic subjects.

However, regimens attempting near normoglycaemia are associated with higher incidence of severe hypoglycaemic episodes. Moreover, injected insulin fails to reproduce the normal pattern of enhanced insulin secretion in response to each meal, and liver is exposed to the same concentration of insulin as other tissues, while normally it receives much higher concentration through portal circulation. As such, the overall desirability and practicability of intensive insulin therapy has to be determined in individual patients. Intensive insulin therapy is best avoided in young children (risk of hypoglycaemic brain damage) and in the elderly (more prone to hypoglycaemia and its serious consequences).

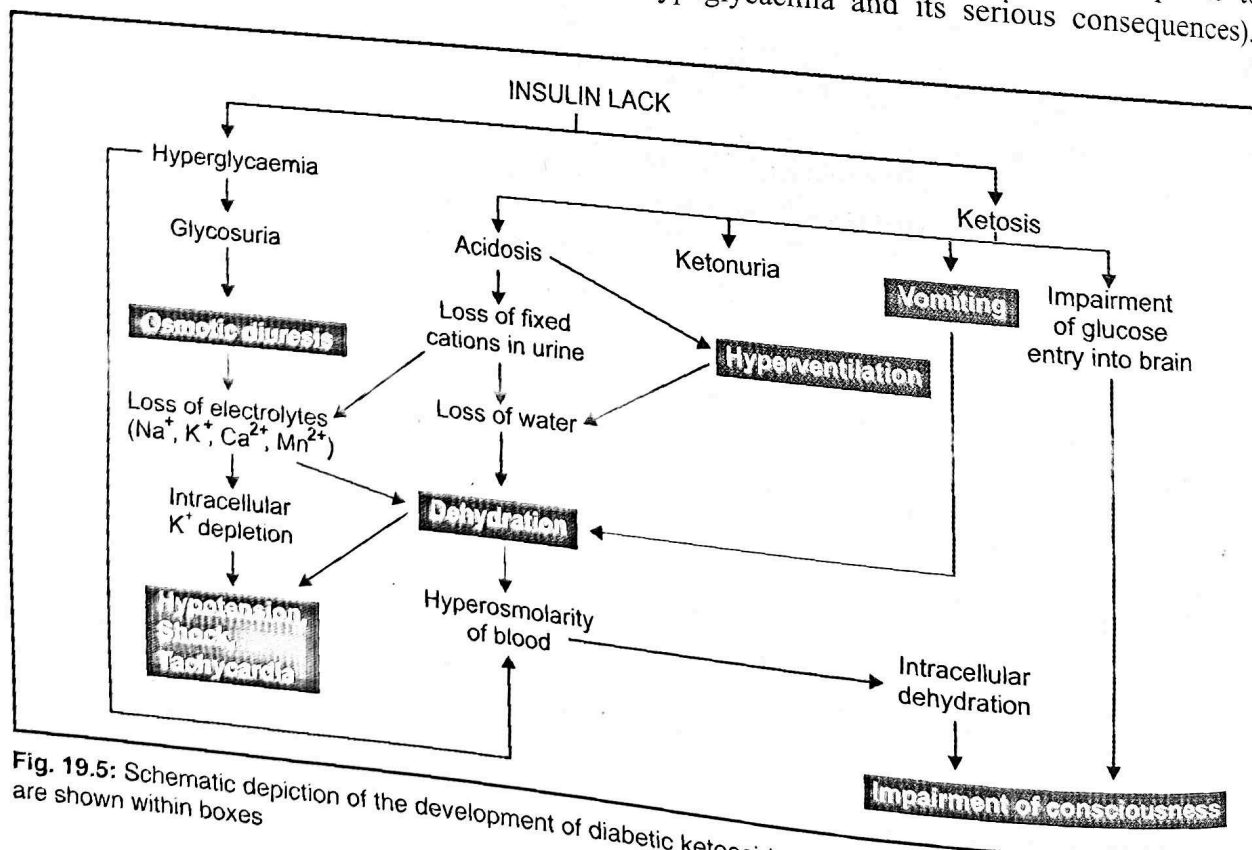


Fig. 19.5: Schematic depiction of the development of diabetic ketoacidosis due to insulin lack. Symptoms produced are shown within boxes

Diabetic ketoacidosis (Diabetic coma)

Ketoacidosis of different grades generally occurs in insulin dependent diabetics, and is due to inadequate/no insulin replacement. It is infrequent in type 2 DM. The most common precipitating cause is infection; others are trauma, stroke, pancreatitis, stressful conditions and inadequate doses of insulin.

The development of cardinal features of diabetic ketoacidosis is outlined in Fig. 19.5. Patients may present with varying severity. Typically they are dehydrated, hyperventilating and have impaired consciousness. The principles of treatment remain the same, irrespective of severity, only the vigour with which therapy is instituted is varied. Close monitoring of vital signs, plasma glucose, blood pH, electrolytes, plasma acetone, etc. is needed.

1. **Insulin** Regular insulin is used to rapidly correct the metabolic abnormalities. A bolus dose of 0.1–0.2 U/kg i.v. is followed by 0.1 U/kg/hr infusion; the rate is doubled if no significant fall in blood glucose occurs in 2 hr. Fall in blood glucose level by 10% per hour can be considered adequate response.

Usually, within 4–6 hours blood glucose reaches 300 mg/dl. Then the rate of infusion is reduced to 2–3 U/hr. This is maintained till the patient becomes fully conscious and routine therapy with s.c. insulin is instituted.

2. **Intravenous fluids** Correction of dehydration is vital. Normal saline is infused i.v., initially at the rate of 1 L/hr, reducing progressively to 0.5 L/4 hours depending on the volume status. Once BP and heart rate have stabilized and adequate renal perfusion is assured change over to $\frac{1}{2}$ N saline. After the blood sugar has reached 300 mg/dl, 5% glucose in $\frac{1}{2}$ N saline is the most appropriate fluid because blood glucose falls before ketones are fully cleared from the circulation. Also glucose is needed to restore the depleted hepatic glycogen.

3. **KCl** Though upto 300 mEq of K^+ may be lost in urine during ketoacidosis, serum K^+ is usually normal due to exchange with intracellular stores. When insulin therapy is

instituted ketosis subsides and K^+ is driven back intracellularly—dangerous hypokalemia can occur. After 2–3 hours it is appropriate to add 10–20 mEq/hr KCl to the i.v. fluid.

4. **Sodium bicarbonate** It is not routinely needed. Acidosis subsides as ketosis is controlled. However, if arterial blood pH is < 7.0 , acidosis is not corrected spontaneously or hyperventilation is exhausting, 50 mEq of sod. bicarbonate is added to the i.v. fluid. Bicarbonate infusion is discontinued when the blood pH rises above 7.1.

5. **Phosphate** When serum PO_4 is in the low-normal range, 3–4 m mol/hr of pot. phosphate infusion is advocated. Faster phosphate infusion can precipitate tetany, and its routine use is not required.

6. **Antibiotics** and other supportive measures as well as treatment of precipitating cause must be instituted simultaneously.

Hyperosmolar (nonketotic hyperglycaemic) coma This is characterized by high blood glucose (>600 mg/dl) and serum osmolality (>320 mOsm/L) along with deteriorating mental status. It generally occurs in elderly type 2 patients. The cause is obscure, but appears to be precipitated by the same factors as ketoacidosis, especially those resulting in dehydration. Uncontrolled glycosuria of DM produces diuresis resulting in dehydration and haemoconcentration over several days. Urine output is finally reduced and glucose accumulates in blood rapidly raising blood osmolality leading to coma. Death can occur if not vigorously treated.

The general principles of treatment are the same as for ketoacidotic coma, except that faster fluid replacement is to be instituted, insulin requirement is lower, less potassium replacement is generally needed and alkali is usually not required. These patients are prone to thrombosis (due to hyperviscosity and sluggish circulation), prophylactic heparin therapy is recommended.

Despite intensive therapy, mortality in hyperosmolar coma remains high. Treatment of precipitating factor and associated illness is vital.

Insulin resistance

Insulin resistance refers to suboptimal response of body tissues, especially liver, skeletal muscle and fat to physiological amounts of insulin. As already stated, relative insulin resistance is integral to type 2 DM. Advanced age, obesity and sedentary life-style promote insulin resistance. Women with polycystic ovarian disease (PCOD) often exhibit insulin resistance.

Insulin sensitivity has been found to decline with age. Obesity is the most important factor causing insulin resistance. Glucose entry into muscle and liver in response to insulin is deficient in individuals with large stores of body fat. Bigger adipocytes have fewer insulin receptors. However, in most type 2 diabetics the transducer mechanism linking insulin receptor to the response appears to be faulty, rather than the receptor itself. Exercise increases insulin sensitivity and lack of it contributes to insulin resistance.

Pregnancy and oral contraceptives often induce relatively low grade and reversible insulin resistance. Other rare causes are—acromegaly, Cushing's syndrome, pheochromocytoma, lipotrophic diabetes mellitus and production of insulin neutralizing antibody. Hypertension accompanied with relative insulin resistance is a part of metabolic syndrome.

Acute insulin resistance This form of insulin resistance develops rapidly and is usually a short term problem. Causes are—

- (a) Infection, trauma, surgery, emotional stress induce release of corticosteroids and other hyperglycaemic hormones which oppose insulin action.
- (b) Ketoacidosis—ketone bodies and FFA inhibit glucose uptake by brain and muscle. In addition insulin binding may increase resulting in insulin resistance.

Treatment of acute insulin resistance is to overcome the precipitating cause and to give high doses of regular insulin. The insulin requirement comes back to normal once the condition has been controlled.

Newer insulin delivery devices A number of innovations have been made to improve ease and accuracy of insulin administration as well as to achieve tight glycaemia control. These are:

1. **Insulin syringes** Prefilled disposable syringes contain specific types or mixtures of regular and modified insulins. These are in common use now, and avoid the need for carrying insulin vials and syringes.
2. **Pen devices** Fountain pen like; they use insulin cartridges for s.c. injection through a needle. Preset amounts (in 2 U increments) are propelled by pushing a plunger. They are convenient in carrying and injecting.
3. **Inhaled insulin** The early inhaled insulin formulations were found to be unsatisfactory for clinical use due to risk of pulmonary complications.

A new dry powder formulation (AFREZZA) of recombinant human insulin called '*Technosphere insulin*' (TI) has been found satisfactory for use in both type 1 and 2 diabetics. Administered by a breath-powered inhaler, it is absorbed from the alveoli and acts rapidly within 10–15 min. The action is terminated by 3 hours. Thus, it is suitable for use just before a meal to control prandial glycaemia. Combined with basal insulin injection (insulin glargine, etc.), it has been found equi-effective in lowering blood glucose and HbA_{1c} levels as prandial insulin aspart injected s.c. (along with basal insulin). Weight gain and risk of hypoglycaemic episodes is claimed to be lower compared to rapid acting s.c. insulin. Cough is the most common adverse effect reported by >25% patients. It is not to be used in smokers and COPD patients.

Another newer inhaled insulin (EXUBERA) has been discontinued by its manufacturer.

4. **Insulin pumps** Portable infusion devices connected to a subcutaneously placed cannula—provide 'continuous subcutaneous insulin infusion' (CSII). Only regular insulin or a fast acting insulin analogue is used. The pump can be programmed to deliver insulin at a low basal rate (approx. 1 U/hr) and premeal boluses (4–15 times the basal rate) to control post-prandial glycaemia. Though, theoretically more appealing, no definite advantage of CSII over multidose s.c. injection has been demonstrated. Moreover, cost, strict adherence to diet, exercise, care of the device and cannula, risk of pump failure, infusion site infection, are too demanding on the patient. The CSII may be appropriate for selected type 2 DM cases only.
5. **Implantable pumps** These consist of an electromechanical mechanism which regulates insulin delivery from a percutaneously refillable reservoir. Mechanical pumps, propellant driven and osmotic pumps have been utilized.

Glucagon-like peptide-1 (GLP-1) receptor agonists

GLP-1 is an important incretin released from the gut in response to ingested glucose. It

induces insulin release from pancreatic β cells, inhibits glucagon release from α cells, slows gastric emptying and suppresses appetite by activating specific GLP-1 receptors, which are cell surface GPCRs (see Fig. 19.6) expressed on β and α cells, central and peripheral neurones, gastrointestinal mucosa, etc. Characteristically, GLP-1 induces insulin release only at high glucose concentration. The incretin system appears to promote β cell health as well by decreasing islet cells apoptosis. Failure of incretins has been implicated in the pathogenesis of β cell dysfunction of type 2 DM, particularly for progression of the disease. GLP-1 based therapy appears to be the most effective measure to preserve β cell function in type 2 DM.

GLP-1 itself is not suitable for clinical use because of rapid degradation by the enzyme *dipeptidyl peptidase-4* (DPP-4) which is expressed on the luminal membrane of capillary endothelial cells, kidney, liver, gut mucosa and immune cells. Another incretin *glucose-dependent insulinotropic peptide* (GIP) also induces insulin release, but in human-beings GLP-1 is the more important incretin and GIP has poor action in type 2 diabetics. The GIP receptor is distinct from GLP-1 receptor, but mediates mostly similar responses. Some metabolically stable analogues of GLP-1 have been produced for clinical use in type-2 DM.

Exenatide It is a synthetic DPP-4 resistant analogue which activates GLP-1 receptors (Fig. 19.6) and produces the same responses. Being a peptide, it is inactive orally. After s.c. injection its plasma $t_{1/2}$ is ~ 3 hours and duration of action 6–10 hours. Injected s.c. before breakfast and dinner, it is used as add-on drug to metformin/SU or a combination of these or pioglitazone in poorly controlled type 2 diabetics. Benefits noted are lowering of postprandial as well as fasting blood glucose, HbA_{1c} , and body weight. The most important side effect is nausea and vomiting occurring in $\sim 50\%$ recipients, but tolerance develops later. Many patients develop antibodies to exenatide, but its response is attenuated only in a few. Acute pancreatitis is a risk.

Dose: Initially 5 μ g s.c. before breakfast and dinner; increase to 10 μ g BD if needed.

EXAPRIIDE 250 μ g/vial inj.

Liraglutide This recently developed longer-acting GLP-1 agonist is closely related to the native peptide but its tight binding to plasma proteins extends $t_{1/2}$ to > 12 hours and duration of action to > 24 hours. Injected s.c. once daily, alone or added to oral metformin $\pm$ SU or pioglitazone, it has achieved improved glycaemic control in type 2 diabetics. Nausea and diarrhoea are the frequent side effects, but decrease in incidence over time. Use of liraglutide is attended by weight loss and it is approved for use in obesity.

Hypoglycaemia is rare with exenatide/liraglutide monotherapy, but can occur when combined with SUs/metformin. Acute pancreatitis is reported in few patients taking GLP-1 agonists.

Albiglutide and *dulaglutide* are very long acting GLP-1 receptor agonists which need to be injected once weekly.

Amylin analogue

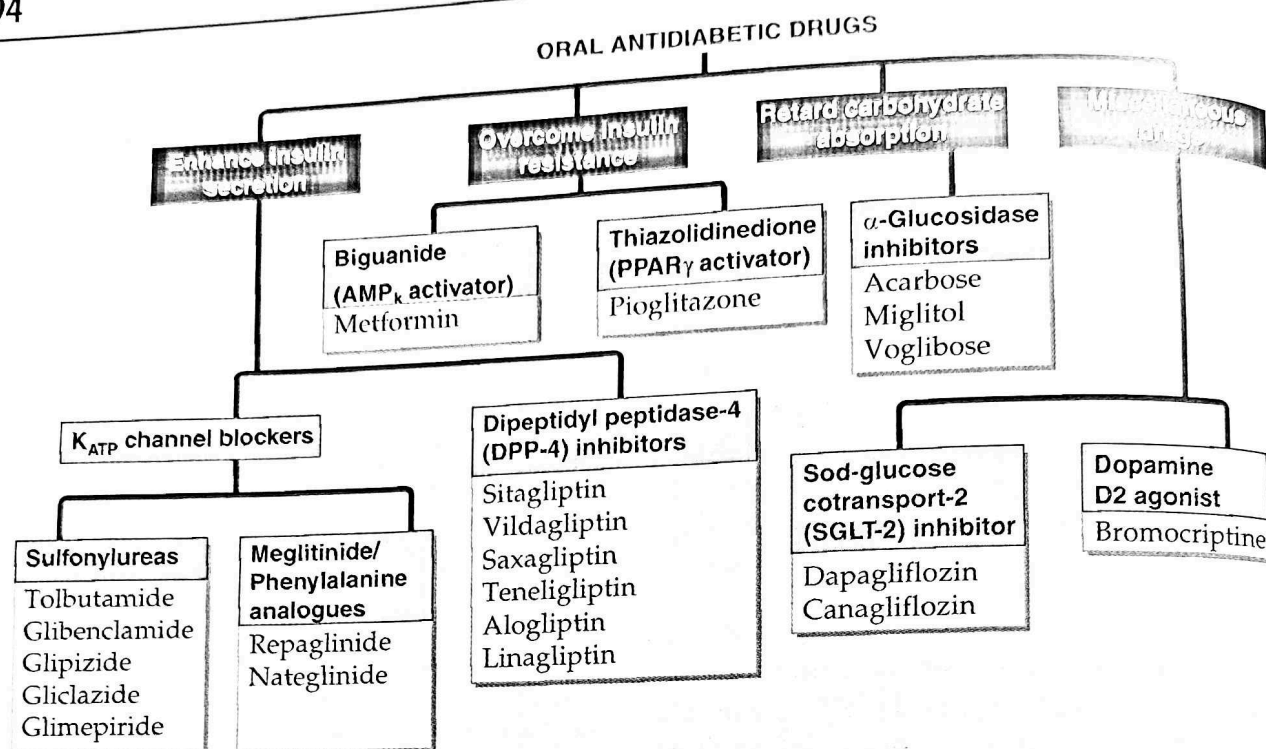
Amylin, also called 'islet amyloid polypeptide' (IAP), is produced by pancreatic β cells and is stored in the same granules as insulin. As such, it is secreted along with insulin, acts in the brain to reduce glucagon secretion from α cells, delay gastric emptying, retard glucose absorption and promote satiety.

Pramlintide It is a synthetic amylin analogue which on s.c. injection before meal attenuates postprandial glycaemia and exerts a centrally mediated anorectic action. The duration of action is 2–3 hours. It is used to supplement meal time insulin injection when insulin alone fails to control postprandial glycaemic peak, in both type 1 and type 2 diabetics. Hypoglycaemia is the most important adverse effect. Loss of appetite, nausea and vomiting are the other side effects. Reduction in body weight is an additional benefit.

ORAL ANTIDIABETIC DRUGS

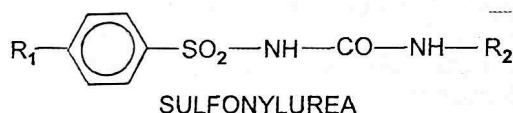
These drugs lower blood glucose levels in diabetics and are effective orally. The chief drawback of insulin is—it must be given by injection. Orally active drugs have always been sought.

The early sulfonamides tested in 1940s produced hypoglycaemia as side effect. Taking this lead, the first clinically acceptable sulfonylurea *tolbutamide* was introduced in 1957. Others followed soon after. In the 1970s many so called 'second generation' sulfonylureas were developed which are >100 times more potent than tolbutamide. Clinically useful biguanide *phenformin* was produced parallel to sulfonylureas in 1957. Newer approaches have constantly been explored and have successively yielded *thiazolidinediones*, *meglitinide analogues*, α -glucosidase inhibitors, *dipeptidyl peptidase-4* (DPP-4) inhibitors and *sod-glucose cotransport* (SGLT-2) inhibitors, etc.



Sulfonylureas (K_{ATP} Channel blockers)

The generic formula of sulfonylureas (SUs) is—



All SUs have similar pharmacological profile, their sole significant action being lowering of blood glucose level in normal subjects and in type 2 diabetics, but not in type 1 diabetics. Being more potent and clinically superior, only the second generation SUs are employed now. All first generation compounds have been discontinued except tolbutamide which is infrequently used.

Mechanism of action Sulfonylureas bind to a specific 'sulfonylurea receptor' (SUR1) located on the pancreatic β cell membrane and provoke a brisk release of insulin, the mechanism of which is detailed in Fig. 19.6. The rate of insulin secretion at any glucose concentration is increased, i.e. insulin release is provoked even at low-glucose concentration risking production of severe and unpredictable hypoglycaemia. In type 2 DM the kinetics of insulin release in

response to glucose or meals is delayed and subdued. The SUs primarily augment the 2nd phase insulin secretion with little effect on the 1st phase. That they do not cause hypoglycaemia in pancreatectomised animals and in type 1 diabetics (presence of at least 30% functional β cells is essential for their action), confirms their indirect action through pancreas.

A minor action reducing glucagon secretion, probably by increasing insulin and somatostatin release has been demonstrated. Hepatic degradation of insulin is also slowed.

Extrapancreatic action After few months of administration, the insulinaemic action of SUs declines, probably due to down regulation of sulfonylurea receptors (SUR1) on β cells, but improvement in glucose tolerance is maintained. In this phase, they sensitize the target tissues (especially liver) to the action of insulin. It is hypothesized that long-term improvement in carbohydrate tolerance leads to overall lowering of circulating insulin concentration which reverses the down regulation of insulin receptors. An apparent increase in their number

Table 19.2: Important features of oral antidiabetics

Drug	Preparations	Plasma $t_{1/2}$ (hr)	Duration of action (hr)	Clearance route*	Daily dose	No. of doses per day	Remarks
SULFONYLUREAS							
1. Tolbutamide	RASTINON, 0.5 g tab.	6	6-8	L	0.5-3 g	2-3	Weaker, shorter acting, flexible dosage, safer in elderly and in those prone to hypoglycaemia.
2. Glibenclamide (Glyburide)	DAONIL, EUGLUCON, BETANASE 2.5, 5 mg tab.	2-4	24	L	2.5-15 mg	1-2	Potent but slow acting, higher incidence of hypoglycaemia, single daily dose despite short $t_{1/2}$ due to active metabolite and sequestration in β cells.
3. Glipizide	GLYNASE, GLIDE, MINIDIAB 5 mg tab	3-5	12	L	5-20 mg	1-2	Fast and shorter acting, higher daily dose to be divided, hypoglycaemia and weight gain less likely, preferable in elderly.
4. Gliclazide	DIAMICRON 80 mg tab. DIAZIDE 20, 80 mg tab GLIZID 30, 40, 80 mg tab	8-20	12-24	L	40-240 mg	1-2	Has antiplatelet action, generates only inactive metabolite, daily dose > 80 mg to be divided.
5. Glimepiride	AMARYL, GLYPRIDE GLIMER 1, 2 mg tab	5-7	24	L	1-6 mg	1-2	Long acting, only inactive metabolite. Stronger extra-pancreatic action.
MEGLITINIDE / PHENYLALANINE ANALOGUES							
1. Repaglinide	EUREPA, RAPLIN, NOVONORM, REGAN 0.5, 1, 2 mg tab	≤ 1	3-5	L	1-8 mg	3-4	Given $\frac{1}{2}$ hr before each meal for limiting post-prandial hyperglycaemia.
2. Nateglinide	GLINATE, NATELIDE 60, 120 mg tab	1.5	2-3	L	180-480 mg	3-4	Stimulates 1st phase insulin secretion, less likely to cause delayed hypoglycaemia.
DPP-4 INHIBITORS							
1. Sitagliptin	JANUVIA 50, 100 mg tab.	~12	24	K	100 mg	1	Non-covalent binding to DPP-4; excreted unchanged in urine. Low risk of hypoglycaemia. Body weight neutral.
2. Vildagliptin	GALVUS, JALRA, ZOMELIS 50 mg cap	2-4	12-24	L, K	50-100 mg	1-2	Covalent binding to DPP-4; Metabolized in liver. Hepatotoxicity reported.
BIGUANIDE							
1. Metformin	GLYCI PHAGE, GLYCOMET 0.5, 0.85 g tab, 0.5 g and 1.0 g SR tabs	1.5-3	6-8	K	0.5-2.5 g	1-2	No hypoglycaemia. Not metabolized. Lactic acidosis rare and only in kidney disease.
THIAZOLIDINEDIONE							
1. Pioglitazone	PIONORM, PIOREST, PIOZONE 15, 30 mg tab	3-5	24	L	15-45 mg	1	May improve lipid profile. Reverses insulin resistance. No hypoglycaemia, C/I in liver and heart disease.

* L—Metabolized in liver; K—Excreted unchanged by kidney

occurs, and/or a post receptor action improves translation of receptor activation.

Pharmacokinetics All SUs are well absorbed orally, and are 90% or more bound to plasma proteins: have low volumes of distribution (0.2–0.4 L/kg). They are primarily metabolized—may produce active metabolite. The metabolites (active/inactive) are excreted in urine. As such, they should be used cautiously in patients with liver or kidney dysfunction.

The distinctive features of different SUs are given in Table 19.2.

Interactions

Drugs that enhance SU action (may precipitate hypoglycaemia) are—

- (a) *Displace from protein binding:* Phenylbutazone, sulfinpyrazone, salicylates, sulfonamides.
- (b) *Inhibit metabolism/excretion:* Cimetidine, ketoconazole, sulfonamides, warfarin, chloramphenicol, acute alcohol intake (also synergises by causing hypoglycaemia).
- (c) *Synergise with or prolong pharmacodynamic action:* Salicylates, propranolol (cardioselective β_1 blockers are less liable), sympatholytic antihypertensives, lithium, theophylline, alcohol (by inhibiting gluconeogenesis).

Drugs that decrease SU action (vitate diabetes control) are—

- (a) *Induce metabolism:* Phenobarbitone, phenytoin, rifampicin, chronic alcoholism.
- (b) *Opposite action/suppress insulin release:* Corticosteroids, thiazides, furosemide, oral contraceptives.

Adverse effects Incidence of adverse effects is quite low (3–7%).

1. **Hypoglycaemia** It is the commonest problem, may occasionally be severe and rarely fatal. It is more common in elderly, liver and kidney disease patients and when potentiating drugs are added. Tolbutamide carries lowest risk due to its low potency and short duration of action.

Treatment of hypoglycaemic episode is to give glucose, may be for a few days because hypoglycaemia may recur.

2. **Nonspecific side effects** Majority of diabetics started on SUs tend to gain 1–3 kg weight. This may be a consequence of insulinaemic action of SUs. Nausea, vomiting, flatulence, diarrhoea or constipation, headache and paresthesias are generally mild and infrequent.

3. **Hypersensitivity** Rashes, photosensitivity, purpura, transient leukopenia, rarely agranulocytosis.

Flushing and a disulfiram-like reaction after alcohol is reported to occur in some individuals taking SUs.

Tolbutamide reduces iodide uptake by thyroid but hypothyroidism does not occur.

Safety of SUs during pregnancy is not established. Change over to insulin is advised. Sulfonyleureas are secreted in milk; they should not be given to nursing mothers.

Meglitinide/D-phenylalanine analogues (K_{ATP} Channel blockers)

These are K_{ATP} channel blockers with a quick and short lasting insulinemic action.

Repaglinide This meglitinide analogue oral hypoglycaemic is designed to normalise meal-time glucose excursions. Though not a sulfonyleurea, it acts in an analogous manner by binding to SUR $\rightarrow$ closure of ATP sensitive K^+ channels $\rightarrow$ depolarisation $\rightarrow$ insulin release (see Fig. 19.6).

Repaglinide is quickly absorbed and rapidly metabolized. It induces fast onset short-lasting insulin release. Because of this characteristic its pattern of use is different from that of SUs. It is administered before each major meal to control postprandial hyperglycaemia; the dose should be omitted if a meal is missed. Because of short lasting action it may have a lower risk of serious hypoglycaemia. Side effects are mild headache, dyspepsia, arthralgia and weight gain.

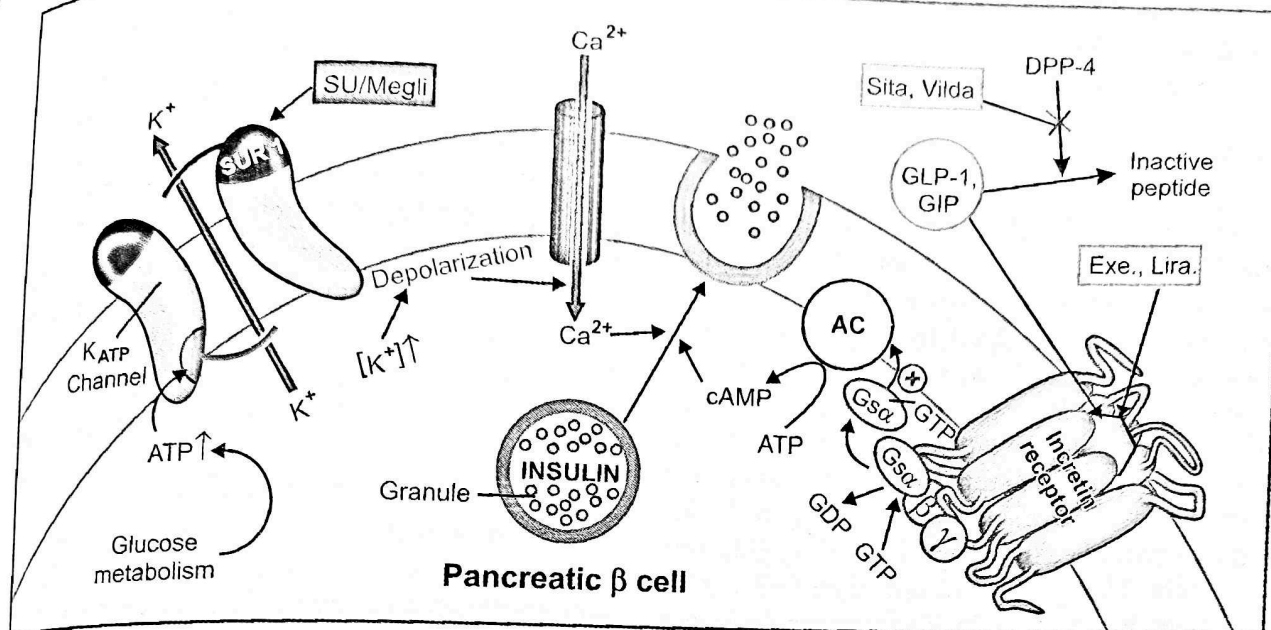


Fig. 19.6: Mechanism of action of insulin secretagogues

The sulfonylureas (SU) and meglitinide analogues (Meglin) act on the sulfonylurea receptor (SUR1) which constitutes a subunit of the inwardly rectifying ATP-sensitive K^+ channel (K_{ATP}) in the membrane of pancreatic β cells. The outward flow of K^+ ions is thereby restricted, intracellular K^+ concentration rises and the membrane is partially depolarized augmenting Ca^{2+} channel opening as well as release of Ca^{2+} from intracellular stores. The Ca^{2+} ions promote fusion of insulin containing intracellular granules with the plasma membrane and exocytotic release of insulin.

Incretins such as glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP) act upon their own G-protein coupled receptors on the β cell membrane to activate adenyl cyclase and generate cAMP, which also promotes exocytosis of insulin. Exenatide (Exe) and liraglutide (Lira) are GLP1 receptor agonists—produce the same response as GLP1. The incretins GLP1 and GIP are rapidly inactivated by the capillary endothelial enzyme dipeptidyl peptidase-4 (DPP-4). Their action is enhanced by DPP-4 inhibitors sitagliptin (sita) and vildagliptin (vilda). The DPP-4 inhibitors thus markedly accentuate the insulin response to ingested glucose/meal and attenuate post-prandial glycaemia.

Repaglinide is indicated only in selected type 2 diabetics who suffer pronounced post-prandial hyperglycaemia, or to supplement metformin/long-acting insulin. It should be avoided in liver disease.

Nateglinide It is a D-phenylalanine derivative which principally stimulates the 1st phase insulin secretion by closing β cell K_{ATP} channels resulting in faster onset and shorter lasting hypoglycaemia than repaglinide. Ingested 10 min before meal, it limits postprandial hyperglycaemia in type 2 diabetics without producing late phase hypoglycaemia. There is little effect on fasting blood glucose level. Episodes of hypoglycaemia are less frequent than with SUs. Side effects are dizziness, nausea, flu-like symptoms and joint pain. It is used in type 2

DM along with other antidiabetics, to control postprandial rise in blood glucose.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Realizing the key role of the enzyme DPP-4 in rapid degradation of endogenous GLP-1, orally active inhibitors of this enzyme have been developed as indirectly acting insulin secretagogues. In the past few years, DPP-4 inhibitors have emerged as important adjunctive drugs in type 2 DM, but their blood sugar lowering efficacy is moderate compared to that of SUs.

Sitagliptin This is the first DPP-4 inhibitor introduced in 2006. It is a competitive and selective DPP-4 inhibitor which potentiates the action of GLP-1 (Fig. 19.6) and GIP, boosts postprandial insulin release, decreases glucagon

secretion and lowers meal-time as well as fasting blood glucose in type 2 diabetics. No effect on gastric emptying and appetite have been noted. It carries low risk of hypoglycaemia unless combined with SUs or insulin, because GLP-1 evokes little insulin release at normal plasma glucose levels. The HbA_{1c} lowering achieved by sitagliptin is almost equivalent to that with metformin. Further lowering of HbA_{1c} by 0.5–1.2% occurs when it is added to pioglitazone/SUs/insulin with or without metformin. However, sitagliptin monotherapy is recommended only when metformin cannot be used. Most professional guidelines recommend DPP-4 inhibitors primarily as adjuvant drugs in type 2 diabetics not well controlled by metformin/SUs/pioglitazone or insulin. Though clinical efficacy of all DPP-4 inhibitors is comparable, one metaanalysis has found sitagliptin to cause greater reduction of fasting blood glucose than vildagliptin.

Sitagliptin is well absorbed orally, is little metabolized and is largely excreted unchanged in urine with a $t_{1/2}$ averaging 12 hours. Dose reduction is needed in renal impairment, but not in liver disease. Sitagliptin is well tolerated, though nausea may occur, it is not prominent as in the case of GLP-1 agonists. It also does not cause weight loss and is body weight neutral. Side effects are nausea, loose stools, headache, rashes, allergic reactions including some serious ones like, angioedema, exfoliative dermatitis and edema. Nasopharyngitis and cough occurs in some patients. Other DPP-4 inhibitors also produce this side effect, which has been ascribed to prevention of substance P degradation. Pancreatitis is reported.

Vildagliptin This DPP-4 inhibitor binds to the enzyme covalently. The complex dissociates very slowly resulting in persistent DPP-4 inhibition even after the free drug has been cleared from circulation. This explains the longer duration of action (12–24 hours) despite short plasma $t_{1/2}$ (2–4 hours). The major route of elimination is by hepatic metabolism; only 20–25% is excreted unchanged in urine. Dose reduction is needed in moderately severe liver and kidney

disease. No significant drug interactions have been reported. Vildagliptin is less selective than sitagliptin for DPP-4; causes some inhibition of DPP-8, DPP-9 as well, but the clinical significance of this feature is not known. The tolerability of vildagliptin is similar to that of sitagliptin, but hepatotoxicity has been reported. Vildagliptin may require twice daily dosing; though single daily dose suffices in most cases when combined with another hypoglycaemic.

Saxagliptin Like vildagliptin, saxagliptin binds covalently with DPP-4 and acts for 24 hours despite a plasma $t_{1/2}$ of 2–4 hours. Added to metformin/SU $\pm$ pioglitazone it causes HbA_{1c} reduction similar to that caused by sitagliptin or vildagliptin. It is metabolized by CYP3A4 and generates an active metabolite that has a $t_{1/2}$ of 3–7 hours. Drug interactions with CYP3A4 inhibitors are possible.

Dose: 5 mg OD; reduce by half in moderately severe renal failure, but not in liver disease.
ONGLYZA 2.5, 5 mg tabs

Teneligliptin It is a new DPP-4 inhibitor developed in Japan which exerts long-lasting (>24 hours) DPP-4 inhibition and antiglycaemic effect. Following a single morning dose, postprandial hyperglycaemia is suppressed at all 3 meals of the day. Therapeutic efficacy both as monotherapy as well as in combination with metformin $\pm$ SUs or a thiazolidinedione is comparable to other gliptins. Metabolites of teneligliptin are excreted by both liver and kidney; no dose reduction is needed in patients with renal impairment. Though no cardiovascular adverse effects have been noted, caution is to be exercised in patients prone to QT prolongation.

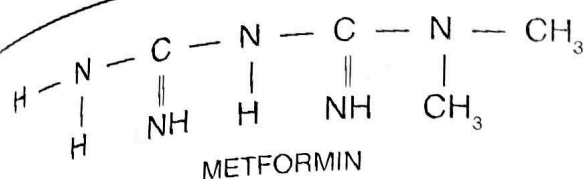
Dose: 20 mg/before breakfast daily, increase to 40 mg/day if needed.

TENGLYN, TENEFIT-20, TENLIMAX 20 mg tab.

Alogliptin and Linagliptin are the other DPP-4 inhibitors.

Biguanide (AMPK activator)

Two biguanide antidiabetics, *phenformin* and *metformin* were introduced in the 1950s. Because of higher risk of lactic acidosis, phenformin has been banned in India since 2003.



Metformin It differs markedly from SUs: causes little or no hypoglycaemia in nondiabetic subjects, and even in diabetics, hypoglycaemia is rare. Thus, it is 'euglycaemic', rather than hypoglycaemic'. It does not stimulate pancreatic β cells. Metformin is reported to improve lipid metabolism as well in type 2 diabetics.

Mechanism of action Biguanides do not cause insulin release, but presence of insulin is essential for their action. Metformin is not effective in pancreatectomized animals and in type 1 diabetics. Though the details are not clear, recent studies have recognized activation of AMP-dependent protein kinase (AMPK) to play a crucial role in mediating the actions of metformin, the key features of which are:

1. Suppresses hepatic gluconeogenesis and glucose output from liver. This is the major action responsible for lowering of blood glucose in diabetics.
2. Enhances insulin-mediated glucose uptake and disposal in skeletal muscle and fat. Insulin resistance exhibited by type-2 diabetics is thus overcome. This translates into—
 - glycogen storage in skeletal muscle
 - reduced lipogenesis in adipose tissue and enhanced fatty acid oxidation.
3. Interferes with mitochondrial respiratory chain and promotes peripheral glucose utilization through anaerobic glycolysis.

AMPK activation by metformin appears to be an indirect consequence of interference with cellular respiration and lowering of intracellular ATP and other energy sources.

Metformin also retards intestinal absorption of glucose, other hexoses, amino acids and Vit B₁₂.

Pharmacokinetics Metformin is well absorbed orally, not metabolized, but excreted unchanged by kidney (Table 19.2). Clearance of metformin approximates g.f.r. It accumulates

in renal failure and increases the risk of lactic acidosis.

Adverse effects Side effects with metformin are frequent, but generally not serious. Abdominal pain, anorexia, bloating, nausea, metallic taste, mild diarrhoea and tiredness are the usual complaints, which tend to subside with time. Metformin does not cause hypoglycaemia except in overdose.

Lactic acidosis Small increase in blood lactate occurs with metformin, but lactic acidosis is rare (<1 per 10,000 patient years) because it is poorly concentrated in hepatic cells. Alcohol ingestion can precipitate lactic acidosis.

Vit B₁₂ deficiency due to interference with its absorption can occur with high dose of metformin.

In addition to general restrictions for use of oral hypoglycaemics (*see below*), metformin is contraindicated in renal insufficiency, because risk of lactic acidosis increases. It should also not be given in hypotensive states, heart failure, severe respiratory/hepatic disease, as well as in alcoholics.

Drugs like cimetidine, furosemide may compete with metformin excretion and enhance its toxicity.

Uses Metformin is now established as a first choice drug for all type 2 DM patients, except when not tolerated or contraindicated.

Advantages of metformin are:

- antihyperglycaemic, but not hypoglycaemic
- weight loss promoting
- has potential to prevent macrovascular as well as microvascular complications of diabetes
- no acceleration of β cell exhaustion/ failure in type 2 DM.
- antihyperglycaemic efficacy (HbA_{1c} reduction by 0.8–1.2%) equivalent to other oral drugs.
- can be combined with any other oral or injectable antidiabetic.
- can prevent new onset type 2 DM in obese, middle aged subjects with impaired glucose tolerance (but not in nonobese older subjects) as shown by the Diabetes Prevention Programme.

The limiting feature is g.i. intolerance, especially at higher doses, but lack of serious toxicity is well established by decades of use.

Infertility: Metformin has been found to improve ovulation and fertility in some infertile women with polycystic ovary. This benefit is observed irrespective of the glycaemic status of the woman; may be due to mitigation of insulin resistance and lowering of circulating insulin levels.

Thiazolidinedione (PPAR γ agonist)

Pioglitazone Only one thiazolidinedione *Pioglitazone* is currently available in India. *Rosiglitazone*, the other member, is banned in India since 2010 and has been withdrawn in Europe due to unacceptable increase in risk of myocardial infarction, CHF, stroke and death. However, a large recent trial failed to confirm such risk, and restrictions on the use of rosiglitazone have been lifted in the USA.

Because of some reports linking pioglitazone with carcinoma of urinary bladder, it was banned in India in June 2013. However, within 2 months the ban was lifted with a warning label 'not to use it as a first line drug'.

This class of oral antidiabetic drugs are selective agonists for the nuclear *peroxisome proliferator-activated receptor γ* (PPAR γ) which is expressed mainly in fat cells, but also in muscle and some other cells. Pioglitazone enhances the transcription of several insulin responsive genes and tends to reverse insulin resistance by enhancing GLUT4 expression and translocation. Entry of glucose into muscle and fat is improved; the primary action is to enhance peripheral insulin sensitivity. Hepatic gluconeogenesis is also suppressed. Activation of genes regulating fatty acid metabolism and lipogenesis in adipose tissue contributes to the insulin sensitizing action. Lipolysis and plasma fatty acid levels are reduced. Adipocyte turnover and differentiation is accelerated by glitazones. Thus, fatty tissue is a major site of their action. The magnitude of blood glucose reduction is somewhat less than SUs and metformin. Improved glycaemic control results in lowering of circulating HbA_{1c} and insulin levels in type 2 DM patients.

Pioglitazone, in addition, lowers serum triglyceride level and raises HDL level without much change in LDL level, probably because it acts on

PPAR α as well to induce expression of reverse cholesterol transporter and some apoproteins.

Pioglitazone is well tolerated; adverse effects are plasma volume expansion, edema, weight gain, headache, myalgia and mild anaemia. Monotherapy with glitazones is not associated with hypoglycaemic episodes. Few cases of hepatic dysfunction have been reported; CHF may be precipitated or worsened. Monitoring of liver function is advised. Pioglitazone is contraindicated in liver disease and in CHF. Glitazones increase the risk of fractures, especially in elderly women.

Pioglitazone is metabolized by both CYP2C8 and CYP3A4. Ketoconazole inhibits and rifampin induces its metabolism. Failure of oral contraception may occur during pioglitazone therapy.

Pioglitazone is indicated in type 2 DM, but not in type 1 DM. It reduces blood glucose and HbA_{1c} (by 0.5–1.2%) without increasing circulating insulin. About 25% patients may not respond (nonresponders), probably due to low baseline insulin levels. It should be stopped if HbA_{1c} reduction is < 0.5% at 6 months. Pioglitazone is primarily used to supplement SUs/metformin and in case of insulin resistance. However, it is not likely to be effective when β cell failure has set in, which may be responsible for loss of efficacy of combination of SUs + metformin. It may also be used as monotherapy (along with diet and exercise) in mild cases.

Several reports describe greater fluid retention, weight gain and precipitation of CHF after combined use of glitazones with insulin. Experts advise avoiding such combination. Pioglitazone should not be used during pregnancy. The Diabetes Prevention Programme (2005) has shown that glitazones have the potential to delay progression of prediabetics to overt type 2 DM. Pioglitazone may help to conserve β cell function in diabetics.

α Glucosidase inhibitors

Acarbose It is a complex oligosaccharide which reversibly inhibits α -glucosidases, the final enzymes for the digestion of carbohydrates

in the brush border of small intestine mucosa. It slows down and decreases digestion and absorption of polysaccharides (starch, etc.) and sucrose. In addition, GLP-1 release is promoted which may contribute to the effect. Postprandial glycaemia is reduced without significant increase in insulin levels. Regular use lowers HbA_{1c} modestly (by 0.4–0.8%), but change in body weight and lipid levels is minimal. The stop-NIDDM trial (2002) has shown that long-term acarbose treatment in prediabetics reduces occurrence of type 2 DM as well as hypertension and cardiac disease. In diabetics, it reduces cardiovascular events.

Acarbose is a mild antihyperglycaemic and not a hypoglycaemic; may be used as an adjuvant to diet (with or without metformin/SU) in obese diabetics. Acarbose 50–100 mg TDS is taken at the beginning of each major meal. Only a small fraction of the dose is absorbed. Flatulence, abdominal discomfort and loose stool are produced in about 50% patients due to fermentation of unabsorbed carbohydrates. Patient acceptability of α -glucosidase inhibitors is poor due to uncomfortable g.i. symptoms. Hepatic transaminases may rise, but liver damage is rare.
GLUCOBAY 50, 100 mg tabs, ASUCROSE, GLUCAR 50 mg tabs.

Miglitol It has a smaller molecule than acarbose, and it is a stronger inhibitor of sucrase. Potency for other α -glucosidases is equivalent to acarbose. Absorption of miglitol is substantial, but variable. The absorbed drug is excreted by the kidney. No systemic toxicity is known.
Dose: 25–100 mg TDS at beginning of each meal.
MIGTOR, DIAMIG, ELITOX 25, 50 mg tabs.

Voglibose Has properties, use and side effects similar to that of acarbose.

Dose: 200–300 μ g TDS just before meals.
VOGLITOR, VOLIX, VOLIBO 0.2, 0.3 mg tabs.

Dopamine D2 agonist

Bromocriptine Recently (2009) a quick release oral formulation of bromocriptine has been approved by US-FDA for adjunctive treatment of type 2 DM. Taken early in the morning it is thought to act on the hypo-

thalamic dopaminergic control of the circadian rhythm of hormone (GH, prolactin, ACTH, etc.) release and reset it to reduce insulin resistance. Bromocriptine can be taken alone to supplement diet+exercise or added to metformin or SU or both. Started at 0.8 mg OD and increased upto 4.8 mg OD (as needed) it has been shown to marginally improve glycaemic control and lower HbA_{1c} by upto 0.5%.

Sodium-glucose co-transport-2 (SGLT-2) inhibitor

Practically all the glucose filtered at the glomerulus is reabsorbed in the proximal tubules. The major transporter which accomplishes this is SGLT-2, whose inhibition induces glucosuria and lowers blood glucose in type 2 DM, as well as causes weight loss.

Dapagliflozin, Canagliflozin These SGLT-2 inhibitors are approved for use in type 2 DM patients. After once daily dosing, they produce round-the-clock glucosuria and lower blood glucose levels. Used alone or in combination with other antidiabetic drugs, they reduce HbA_{1c} levels by 0.5–1.0%, but do not cause hypoglycaemia. The concerns which appear inbuilt due to their mechanism of action are—glycosuria which can predispose to urinary and genital infections, electrolyte imbalance, ketoacidosis and increased urinary frequency. They are contraindicated in patients with renal insufficiency. Other long term safety concerns have also been raised.

Bile acid sequestrant

Colesevelam It is a bile acid binding resin which lowers cholesterol as well as glucose levels in blood. It is approved as add-on drug in type 2 DM patients who are not properly controlled by other antidiabetic drugs. The mechanism of action is not clear, but may involve reduction in farnesoid X receptor (FXR) activation. The HbA_{1c} lowering efficacy of colesevelam is modest, and g.i. upset is frequent.

Status of oral antidiabetics in diabetes mellitus

After 8 years of prospective study involving large number of patients, the University Group Diabetes Programme (UGDP) of USA (1970) presented findings that cardiovascular mortality was higher in patients treated with biguanides and SUs than in those treated with diet and exercise alone or with insulin. A decline in the use of oral hypoglycaemics followed. Subsequent studies both refuted and supported these conclusions.

The controversy was settled by the UK PDS trial which found that both SUs and metformin did not increase cardiovascular mortality

over > 10 years observation period. Related to degree of glycaemia control, both insulin and SUs reduced microvascular complications (retinopathy, neuropathy, nephropathy) in type 2 DM, but did not have significant effect on macrovascular complications (coronary artery disease, stroke, etc). Metformin, however, could reduce both microvascular as well as macrovascular complications. It decreased risk of death and other diabetes related endpoints in overweight patients. This may be related to the fact that both SUs and exogenous insulin improve glycaemic control by increasing insulin supply rather than by overcoming insulin resistance, while metformin can decrease insulin resistance which is a pathogenic factor in type 2 DM. All oral hypoglycaemics do however control symptoms that are due to hyperglycaemia and glycosuria, and are much more convenient to use than insulin.

Oral antidiabetics are indicated only in type 2 diabetes, in addition to diet and exercise. They are most effective in patients with—

1. Age above 40 years at onset of disease.
2. Obesity at the time of presentation.
3. Duration of disease < 5 years when starting treatment.
4. Fasting blood sugar < 200 mg/dl.
5. Insulin requirement < 40 U/day.
6. No ketoacidosis or a history of it, or any other complication.

The Diabetes Prevention Programme (2002) has established that in middle aged, obese prediabetics metformin prevented progression to type 2 DM, but not in older nonobese prediabetics. Glitazones also appear to have prophylactic potential. Long-term acarbose therapy as well can delay type 2 DM.

Oral antidiabetics should be used to supplement dietary management and not to replace it. In view of the prophylactic and outcome benefits, current recommendation is to institute metformin therapy right at the diagnosis of type 2 DM, along with dietary and other lifestyle measures, without waiting to see if the latter alone are sufficient. Metformin may delay progression of diabetic severity by

favourably affecting β cell health and retarding β cell failure. It is especially valuable for obese patients, because it may also aid weight reduction. Further, it has the potential to reduce the risk of myocardial infarction and stroke. Thus, unless contraindicated or not tolerated, metformin is prescribed to all type 2 diabetics, despite its inferior patient acceptability due to g.i. side effects.

Many type 2 DM patients do not attain the target level of glycaemia control and HbA_{1c} reduction (to < 7%) with metformin alone, and a second drug is needed. SUs are the most commonly selected 2nd drug. They have good patient acceptability, convenient dosing and high efficacy, but can cause weight gain and hypoglycaemia. There is some evidence that SUs given over long-term (2–10 years) expedite β cell apoptosis and failure. Receptor desensitization may also be a cause, and SUs tend to lose efficacy in few years (5–10% per year failure rate). There is no difference in the clinical efficacy of various 2nd generation SUs. However, this does not indicate that choice among them is irrelevant. Differences among them are mainly in dose, onset and duration of action which govern flexibility of regimens. Some specific features of various SUs are given in Table 19.2. If a particular SU proves inadequate in a given patient, another one may still work.

Patients with near normal fasting blood glucose but prominent post-prandial hyperglycaemia, or those experiencing late postmeal hypoglycaemia may do better with premeal repaglinide or nateglinide.

Pioglitazone is usually the 3rd choice drug; may be added to metformin or a combination of metformin + SU. It is particularly useful for patients with prominent insulin resistance. Though it tends to preserve β cell function and does not cause hypoglycaemia, it is rarely selected for monotherapy. Its major limitations are—tendency to fluid retention, weight gain, increased risk of heart failure and fractures, and need to monitor liver function. Moreover, it is ineffective in a significant number of patients.

Acarbose-like drugs are mild antihyperglycaemics, mostly used as supplementary drugs to a hypoglycaemic regimen. They are disliked by many patients because of bloating, indigestion and other abdominal symptoms.

The newer oral antidiabetics that have gained popularity now are the DPP-4 inhibitors. Their favourable features are:

- Insulin release is glucose dependent (occurs only at high glucose concentrations) therefore not likely to induce hypoglycaemia.
- Suppress glucagon release, thus lowering fasting blood glucose level as well.
- Improve β cell health and retard progression of β cell failure.
- Body weight neutral.
- Can be used in patients with renal impairment.
- Mostly single daily dose, well tolerated with few side effects, no drug interactions, except with saxagliptin.

However, the DPP-4 inhibitors cause moderate HbA_{1c} lowering compared to SUs and some serious reactions like angioedema, Stevens-Johnson syndrome, anaphylaxis have been reported. Moreover, they are relatively new drugs and have not withstood the test of time yet. Their impact on cardiovascular mortality and other outcomes is yet to be established. As such, most professional guidelines place them as second line/add on antidiabetic drugs. They are especially valuable for patients having body weight problem and those experiencing frequent episodes of hypoglycaemia.

The SGLT-2 inhibitors (e.g. dapagliflozin) are the newest class of oral drugs that may be considered for addition to a combination oral antidiabetic regime when the latter fails to achieve the target HbA_{1c} level. They predispose to urinary tract infections, genital fungal infections, hypovolaemia and have other limitations.

Upto 50% patients of type 2 DM initially treated with oral antidiabetics ultimately need insulin. Moreover, when a diabetic on oral antidiabetics presents with infection, severe trauma or stress, pregnancy, ketoacidosis or any other complication, or has to be operated upon—switchover to insulin (see Flow chart in Fig. 19.7). Metformin alone or in combina-

tion with SUs or DPP-4 inhibitors is usually continued with insulin, particularly when a single daily injection of long-acting (e.g. glargine) insulin is used to provide basal control. The oral drug given before meals serves to check postprandial glycaemia, while metformin mainly reduces hepatic glucose output.

The GLP-1 agonists (exenatide/liraglutide injected s.c.) are an alternative to insulin in obese type 2 diabetics in whom weight gain is to be avoided. They help weight reduction and are unlikely to induce hypoglycaemia. Frequent nausea and risk of pancreatitis are their drawbacks.

Epalrestat Sorbitol is a minor metabolite of glucose generated by the enzyme *aldose reductase*. In diabetics, excess sorbitol is produced and gets deposited in nerves and other tissues. This is involved in the pathogenesis of diabetic neuropathy and other complications. *Epalrestat* is an aldose reductase inhibitor developed in Japan which has been found to delay sorbitol accumulation in sciatic nerve/other tissues of diabetics imparting potential to delay progression of diabetic neuropathy. In trials it has caused modest improvement in nerve conduction, neuropathic pain and other symptoms. However, magnitude of benefit and safety are yet to be defined. Nausea, vomiting and elevation of liver enzymes are the adverse effects.

Dose: 50 mg TDS before meals; ALRISTA 50 mg tab.

GLUCAGON

A hyperglycaemic principle was demonstrated to be present in the pancreatic islets just two years after the discovery of insulin in 1921. It was named 'glucagon'. Glucagon is a single chain polypeptide containing 29 amino acids, MW 3500. It is secreted by the α cells of the islets of Langerhans and commercially produced now by recombinant DNA technology.

Regulation of Secretion Like insulin, glucagon is also derived by cleavage of a larger peptide prohormone. Its secretion is regulated by glucose levels, other nutrients, paracrine hormones and nervous system. Glucose has opposite effects on insulin and glucagon release, i.e. high glucose level inhibits glucagon secretion. The incretin GLP-1, FFA and ketone bodies also inhibit glucagon release. Amino acids, however, induce both insulin and glucagon secretion. Insulin, amylin and somatostatin, elaborated by the neighbouring β and δ cells, inhibit glucagon secretion. Sympathetic stimulation consistently and parasympathetic stimulation under certain conditions evokes glucagon release.

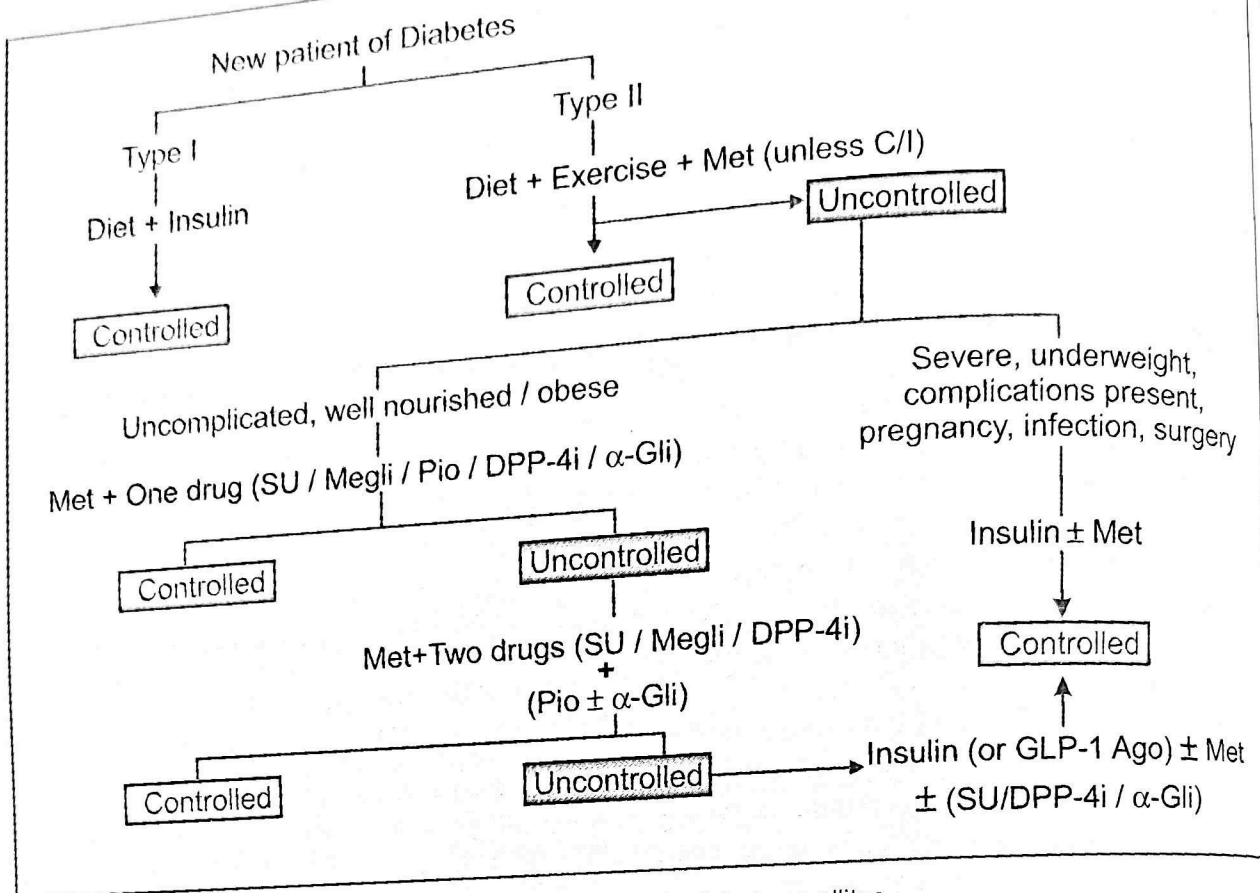


Fig. 19.7: Simplified flow chart of management approaches in diabetes mellitus
 Met—Metformin; SU—Sulfonylurea; Megli—Meglitinide/d-phenylalanine analogue; DPP-4i—Dipeptidyl peptidase-4 inhibitor; α Gli—α Glucosidase inhibitor; Pio—Pioglitazone; GLP-1 Ago—GLP-1 receptor agonist.
 Note: A meglitinide drug is indicated only in patients with predominant postprandial hyperglycaemia.
 An α glucosidase inhibitor can be additional add on drug.

Actions Glucagon is hyperglycaemic; most of its actions are opposite to that of insulin. Glucagon causes hyperglycaemia primarily by enhancing glycogenolysis and gluconeogenesis in liver. Suppression of glucose utilization in muscle and fat contributes modestly. Glucagon is considered to be the hormone of fuel mobilization. Its secretion is increased during fasting, and is largely responsible for the high fasting blood glucose levels in type 2 diabetics. It plays an essential role in the development of diabetic ketoacidosis. Increased secretion of glucagon has been shown to attend all forms of severe tissue injury.

Glucagon increases the force and rate of cardiac contraction and this is not antagonized by β blockers. It has a relaxant action on the gut and inhibits gastric acid production.

Mechanism of action Glucagon, through its own receptor and coupling Gs protein activates adenylyl cyclase and increases cAMP in liver, fat cells, heart and

other tissues; most of its actions are mediated through this cyclic nucleotide.

Glucagon is inactive orally; that released from pancreas is broken down in liver, kidney, plasma and other tissues. Its plasma $t_{1/2}$ is 3–6 min.

Uses

1. **Hypoglycaemia** Use of glucagon to counteract insulin/oral hypoglycaemic drug induced hypoglycaemia is only an expedient measure for the emergency, and must be followed by oral glucose/sugar given repeatedly till the blood glucose level stabilizes. It may not work if hepatic glycogen is already depleted.

Dose: 0.5–1.0 mg i.v. or i.m.

GLUCAGON 1 mg inj.

2. **Cardiogenic shock** Glucagon may be used to stimulate the heart in β adrenergic blocker treated patients. However, action is not very marked.

Other hyperglycaemics

Diazoxide Chemically related to thiazides, it inhibits insulin release from β cells and causes hyperglycaemia lasting 4–8 hours. Its action on ATP sensitive K^+ channels of β cells is opposite to that of SUs. Other actions which may contribute to hyperglycaemia are decreased peripheral utilization of glucose and release of catecholamines. It has been used to prevent hypoglycaemia in

insulinomas. Other actions are vasodilatation, fall in BP and antidiuresis.

Somatostatin It causes hyperglycaemia primarily by inhibiting insulin release.

Streptozocin It is obtained from *Streptomyces achromogenes*. Causes selective damage to insulin secreting β cells. It has been used to produce experimental diabetes in animals and to treat insulin secreting tumours of pancreas.

PROBLEM DIRECTED STUDY

19.1 During routine medical checkup a 50-year male office executive with sedentary lifestyle was diagnosed to have developed type 2 diabetes mellitus. His fasting and post-meal blood glucose was 130 mg/dl and 190 mg/dl respectively, HbA_{1c} was 7.8%, BP was 130/82 mm Hg and body mass index was 27 kg/m². He was asymptomatic and investigations revealed no end organ damage. He was advised suitable diet, exercise and other lifestyle modifications.

(a) Should he be prescribed an antidiabetic medication as well? If so, which drug/combination of drugs should be selected, and why?

(see Appendix-1 for solution)