Diabetes mellitus DM.

Anti-diabetic drugs

Provided that pharmacologic therapy is not required immediately (***FPG < 250 mg/dL***), all newly diagnosed patients should be given at least a 1-month trial of diet,exercise, and weight management. If this regimen does not lead to adequate blood glucose control, the physician will need to prescribe oral or subcutaneous antihyperglycemic agents or insulin, or both.Various drugs are effective in reducing hyperglycaemia in patients with type 2 diabetes. Although their mechanisms of action are different, most depend upon a supply of endogenous insulin and therefore have little hypoglycaemic effect in patients with type 1 diabetes. The insulin secretagogues (***sulfonylureas, meglitinides, and d-phenylalanine derivatives***) have similar mechanisms of action and may cause hypoglycemia, hence the term oral hypoglycemic agents.The other classes of noninsulin agents each target a different pathologic process and are referred to as antihyperglycemic agents. ***Metformin and sulphonylureas*** have been the mainstay of treatment for many years and have the strongest evidence of preventing complications of diabetes.

Biguanides

Metformin is the only biguanide available. it is now widely used as first-line therapy for type 2 diabetes, irrespective of body weight. Metformin is also used increasingly as an adjunct to insulin therapy in obese patients with type 1 diabetes. However, it is less well tolerated than sulphonylureas because of a higher incidence of side-effects, particularly gastrointestinal symptoms.

Mechanism of action

The mechanism of action of metformin has not been precisely defined. It has ***no hypoglycaemic effect in non-diabetic individuals***, but in diabetes, insulin sensitivity and peripheral glucose uptake ***are increased***, possibly through ***inhibition*** of mitochondrial respiration and activation of AMP-regulated kinase (AMPK) in muscle. There is some evidence that it also ***impairs*** glucose absorption by the gut and ***inhibits*** hepatic gluconeogenesis. Although secretion of some endogenous insulin is mandatory for its glucose-lowering action, it does not increase insulin secretion and seldom causes hypoglycaemia.

Indications for use

Administration of metformin is ***not associated*** with a rise in body weight and it may be beneficial for the ***overweight or obese*** patient. It can be given in combination with most other anti-diabetic medications.
Metformin is given with food, usually starting with 500 mg 12-hourly, gradually increased as required to a maximum of 1 g 8-hourly.

Metformin can ***increase susceptibility*** to lactic acidosis. Its use is contraindicated in patients with ***impaired renal or hepatic function and in those who drink alcohol in excess in whom the risk of lactic acidosis is significantly increased.*** It should be discontinued, at least temporarily, if any other serious medical condition develops, especially one causing severe shock or hypoxaemia.

Insulin secretagogues—agents that affect the ATP-sensitive K+ Channel and increase insulin secretion ;

Mechanism of action

Sulphonylureas are 'insulin secretagogues' that act through a specific receptor which is linked to a K+ channel on the surface of pancreatic β cells. its principal action the stimulation of endogenous insulin secretion from the pancreatic β cells. The drugs in this class also increase β-cell sensitivity to glucose and exert some influence in diminishing insulin resistance.

.a-*First-generation sulfonylureas*

Sulphonylureas are valuable in the treatment of ***non-obese patients with type 2 diabetes*** who fail to respond to dietary measures alone. Although sulphonylureas will lower the blood glucose concentration of obese patients with type 2 diabetes, such patients should be treated energetically in the first instance by dietary measures with or without metformin, since treatment with sulphonylureas is often associated with an increase in weight which will exacerbate insulin resistance.

The main differences between the individual compounds lie in their potency, duration of action and cost. ***Tolbutamide***, the mildest of the first-generation sulphonylureas, is very well tolerated. Its duration of action is relatively short, it is usually administered 8- or 12-hourly, and it is a useful drug in the elderly in whom the risk and the consequences of inducing hypoglycaemia are greater. ***Chlorpropamide*** has a biological half-life of about 36 hours and is taken once daily, but may cause severe and prolonged hypoglycaemia and is rarely used.

*b-**Second-generation sulfonylureas***; have a more rapid onset of action and better coverage of the postprandial glucose rise, but the shorter half-life of some agents may require more than once-a-day dosing. Of the second-generation sulphonylureas, ***gliclazide*** and glipizide cause few side-effects, but ***glibenclamide*** is prone to induce severe hypoglycaemia and should be avoided in the elderly. Newer long-acting preparations such as ***glimepiride*** and a modified-release form of gliclazide can be administered once daily with no apparent increased risk of hypoglycaemia.

Most sulfonylureas are metabolized in the liver to compounds (some of which are active) that are cleared by the kidney. Thus,their use in individuals with significant hepatic or renal dysfunction is not advisable. Weight gain, a common side effect of sulfonylurea therapy, results from the increased insulin levels and improvement in glycemic control.

Several drugs can potentiate the hypoglycaemic effect of sulphonylureas by displacing them from their plasma protein-binding sites, e.g. salicylates, warfarin, phenylbutazone and antifungal agents like fluconazole.

c-Nonsulfonylureas; Repaglinide, nateglinide, and mitiglinide are not sulfonylureas but also interact with the ATP-sensitive potassium channel. Repaglinide directly stimulates endogenous insulin secretion through the sulphonylurea receptor and is taken immediately before food. It is ***less likely*** to cause hypoglycaemia than sulphonylureas. Nateglinide has a similar mode of action, restores first-phase insulin secretion, and can be prescribed with metformin.

Alpha-glucosidase inhibitors

The α-glucosidase inhibitors delay carbohydrate absorption in the gut by selectively ***inhibiting disaccharidases***. Acarbose and miglitol are available and are taken with each meal. Both lower post-prandial blood glucose and modestly improve overall glycaemic control. They can be combined with a sulphonylurea. The main side-effects are ***flatulence, abdominal bloating and diarrhoea.***

Insulin secretagogues¬agent that enhance GLP-1 receptor or signaling

The secretion of insulin in response to a rise in blood glucose is greater when glucose is given by mouth than by intravenous infusion. In part this is caused by secretion of gut hormones, or incretins, which potentiate glucose-induced insulin secretion. Glucagon-like peptide (GLP-1) is an incretin hormone which stimulates insulin secretion in a glucose-dependent manner; thus hypoglycaemia does not occur. In addition, GLP-1 suppresses glucagon secretion, delays gastric emptying, reduces appetite and encourages weight loss.

As GLP-1 is rapidly degraded by the enzyme, dipeptidyl peptidase 4, inhibitors of this enzyme can be used to prolong its biological effect. The DPP-4 inhibitors or gliptins (sitagliptin, vildagliptin and saxagliptin) are oral agents which act in this manner. They are weight-neutral and have few side-effects.

Incretin-based therapies are most useful in obese patients and can be used in combination with other oral anti-diabetic agents.

Thiazolidinediones

Mechanism of action

TZDs enhance the actions of endogenous insulin, partly directly (in the adipose cells) and partly indirectly (by altering release of 'adipokines' such as adiponectin and resistin which alter insulin sensitivity in the liver). Plasma insulin concentrations are not increased and hypoglycaemia does not occur.

Indications for use

Pioglitazone or rosiglitazone are usually prescribed as second-line therapy with metformin, or as third-line therapy in combination with sulphonylurea and metformin (known as 'triple therapy'). However, their use as monotherapy and in combination with insulin is increasing.

TZDs are most likely to be effective in patients with pronounced insulin resistance (e.g. in abdominal obesity) and redistribute fat away from the abdominal stores and into subcutaneous depots.

TZDs have significant side-effects. The first drug of this class, troglitazone, had to be withdrawn because of hepatotoxicity and newer TZDs are avoided in patients with liver dysfunction, but it appears that this effect was specific to troglitazone. An important side-effect of all TZDs is sodium and fluid retention, which is aggravated if they are combined with insulin.
TZDs must be avoided in patients with cardiac failure. They also increase upper limb fractures, mainly in women.

Sodium-Glucose Co-Transporter 2 Inhibitors (SLGT2)

These agents lower the blood glucose by selectively inhibiting this co-transporter, which is expressed almost exclusively in the proximal,convoluted tubule in the kidney. This inhibits glucose reabsorption,lowers the renal threshold for glucose, and leads to increased urinary glucose excretion. Thus, the glucose-lowering effect is insulin independent and not related to changes in insulin sensitivity or secretion. Because these agents are the newest class to treat type 2 DM, clinical experience is limited. Due to the increased urinary glucose, urinary or vaginal infections are more common, and the diuretic effect can lead to reduced intravascular volume.

Insulin therapy

Manufacture and formulation

Insulin was discovered in 1921 and transformed the management of type 1 diabetes. Until the 1980s insulin was obtained by extraction and purification from pancreata of cows and pigs (bovine and porcine insulins), and some patients still prefer to use animal insulins. Recombinant DNA technology enabled large-scale production of human insulin. More recently, the amino acid sequence of insulin has been altered to produce analogues of insulin, which differ in their rate of absorption from the site of injection.
The duration of action of short-acting, unmodified insulin ('soluble' or 'regular' insulin), which is a clear solution, can be extended by the addition of protamine and zinc at neutral pH (isophane or NPH insulin) or excess zinc ions (lente insulins).

Duration of action (in hours) of insulin preparations

Insulin	Onset	Peak	Duration
Rapid-acting (insulin analogues: lispro, aspart, glulisine)	< 0.5	0.5-2.5	3-4.5
Short-acting (soluble (regular))	0.5-1	1-4	4-8
Intermediate-acting (isophane (NPH), lente)	1-3	3-8	7-14
Long-acting (bovine ultralente)	2-4	6-12	12-30
Long-acting (insulin analogues: glargine, detemir)	1-2	None	18-24

Subcutaneous multiple dose insulin therapy

In most patients, insulin is injected subcutaneously several times a day into the anterior abdominal wall, upper arms, outer thighs and buttocks. Accidental

intramuscular injection often occurs in children and thin adults.
The rate of absorption of insulin may be influenced by many factors other than the insulin formulation, including the site, depth and volume of injection, skin temperature (warming), local massage and exercise. Absorption is delayed from areas of lipohypertrophy at injection sites , which results from the local trophic action of insulin, so repeated injection at the same site should be avoided. Other routes of administration (intravenous and intraperitoneal) are reserved for specific circumstances.

Short-acting insulin has to be injected at least 30 minutes before a meal to allow adequate time for absorption. Many patients find this inconvenient and ignore this requirement. However, the rapidly absorbed fast-acting insulin analogues can be administered immediately before, during or even after meals, and their peak action coincides more closely with the post-prandial rise in blood glucose .

Once absorbed into the blood, insulin has a half-life of a few minutes. It is removed mainly by the liver and also the kidneys; plasma insulin concentrations are elevated in patients with liver disease or renal failure. The rate of clearance is also affected by binding to insulin antibodies (associated with the use of animal insulins).

A common problem that associated with the use of insulins is fasting hyperglycaemia (***'the dawn phenomenon***') associated with the normal circadian rhythm and causing release of counter-regulatory hormones during the later part of the night, which antagonise insulin action before wakening.

Side-effects of insulin therapy

1. Hypoglycemia
2. Weight gain
3. Peripheral oedema (insulin treatment causes salt and water retention in the short term)
4. Insulin antibodies (animal insulins)
5. Local allergy (rare)
6. Lipodystrophy at injection sites.

Insulin dosing regimens

The choice of regimen depends on the desired degree of glycaemic control, the severity of underlying insulin deficiency, the patient's lifestyle, and his or her ability to adjust the insulin dose. Most people require two or more injections of insulin daily. Once-daily injections rarely achieve satisfactory glycaemic control and are reserved either for some elderly patients or for those who retain substantial endogenous insulin secretion and have a low insulin requirement.

Twice-daily administration of a short-acting and intermediate-acting insulin (usually soluble and isophane insulins), given in combination before breakfast

and the evening meal, is the simplest regimen and is still used commonly. Individual doses vary considerably but usually two-thirds of the total daily requirement of insulin is given in the morning in a ratio of 1:2, short-:intermediate-acting insulins. The remaining third is given in the evening, and doses are adjusted according to blood glucose measurements. Several pre-mixed formulations are available containing different proportions of soluble and isophane insulins (e.g. 30:70 and 50:50). These are useful for patients who have difficulty mixing insulins, but are inflexible as the individual components cannot be adjusted independently, and require to be resuspended by shaking the vial several times before administration.

Multiple injection regimens are popular, with short-acting insulin being taken before each meal (usually by en injector), and intermediate- or long-acting insulin being injected once or twice daily (basal-bolus regimen). This type of regimen allows greater freedom of timing of meals and more variable day-to-day physical activity, but snacks may have to be taken between meals to prevent hypoglycemia.

Alternative insulin therapies

'Open-loop' systems are battery-powered portable pumps providing continuous subcutaneous or intravenous infusion of insulin without reference to the blood glucose concentration.

Alternative routes of insulin delivery have been investigated. Intrapulmonary insulin by inhalation for the treatment of type 2 diabetes is effective, but has not been commercially viable and may be associated with an increased risk of lung cancer. Transdermal and even oral insulin therapies are being explored.

Combined oral anti-diabetic therapy and insulin

In patients with type 2 diabetes who are requiring increasing doses of oral anti-diabetic drugs, the introduction of a single dose of an intermediate- (e.g. isophane) or long-acting insulin analogue, administered at bedtime, may improve glycaemic control and delay the development of overt pancreatic β-cell failure. The exogenous insulin suppresses hepatic glucose output during the night and lowers fasting blood glucose. This treatment is ineffective in diabetic patients who have no residual endogenous insulin secretion. The combination of bedtime isophane insulin with metformin is the regimen least likely to promote weight gain.

Transplantation

Whole pancreas transplantation is carried out in a small number of patients with diabetes each year, but it presents problems relating to the exocrine pancreatic secretions and long-term immunosuppression is necessary.