

# Everyday Practice: Diabetes Mellitus

## Management of type 2 diabetes mellitus with oral antihyperglycaemic therapy

ANKUSH DESAI, NIKHIL TANDON

### INTRODUCTION

Management of type 2 diabetes mellitus (DM) encompasses 3 major strategies:

1. *Medical nutrition therapy and lifestyle modification.* This involves modification of diet, exercise and physical activity and other practices with the aim of improving metabolic control and cardiovascular health.
2. *Use of anti-diabetic drugs.* Various drugs (both oral and parenteral) have been approved for the management of DM and form the mainstay of therapy for type 2 DM.
3. *Insulin.* Insulin and its analogues in various regimens are used for the control of hyperglycaemia in all forms of DM.

Medical nutrition therapy has been covered in an earlier article in the series (Patil M. Nutrition therapy and exercise. *Natl Med J India* 2007;20:142–6), while insulin treatment in type 2 DM will be dealt with in a subsequent article. In this article, we will restrict ourselves to various oral antidiabetic drugs (OADs) and newer parenteral antihyperglycaemic agents used in clinical practice.

### PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

Type 2 DM is a metabolic disorder resulting from a relative deficiency of insulin secretion and variable degree of decreased insulin action, or insulin resistance. Insulin resistance primarily occurs at the skeletal muscle and adipose tissue. When confronted with insulin resistance, initially there is a compensatory increase in pancreatic insulin secretion to ensure euglycaemia. Further in the natural history of the disease, insulin secretion declines, leading to progressive hyperglycaemia. This occurs initially in the postprandial state and later with failure of suppression of hepatic glucose production by declining levels of insulin, even in the fasting state. These pathophysiological lesions are the favoured targets for pharmacological therapy.

### HISTORY OF ORAL ANTIDIABETIC DRUGS (OADs)

Though fenugreek and zedoary seeds have been recommended for DM for many centuries, the first orally active drug for DM appeared only after the discovery of insulin. Synthalin, a guanidine derivative, was introduced in the year 1926, but soon withdrawn due to toxicity.

Sulphonylureas came into clinical practice following the work done by Celestino Ruiz and Auguste Loubatieres, who observed the glucose-lowering action of sulphonamides in intact but not in

pancreatectomized animals in the early 1940s. Carbutamide was introduced in 1955, followed 2 years later by tolbutamide. Subsequently, various agents of the same group were discovered including chlorpropamide, glibenclamide, glipizide, gliclazide and glimepiride. The non-sulphonylureas, repaglinide and nateglinide were introduced in the late 1990s following research on the K<sup>+</sup>-ATP channels.

The first biguanide in clinical use was phenformin (in 1957) and was followed soon by metformin and buformin. Buformin was withdrawn quickly and phenformin met the same fate in the 1970s due to a high risk of fatal lactic acidosis. Presently, metformin is the only biguanide available for clinical use.

Thiazolidinediones, the peroxisome proliferator-activated receptor (PPAR) agonists, have been studied since the 1980s for their antihyperglycaemic effects. Troglitazone, the first agent to be introduced in 1997 was soon withdrawn due to risk of fulminant hepatic failure. Pioglitazone and rosiglitazone were launched in 1999, and are currently in clinical use.

Role of the gut in carbohydrate metabolism was exploited by designing agents which retard the breakdown of complex carbohydrates, thereby delaying their absorption. Acarbose was the initial  $\alpha$ -glucosidase inhibitor (AGIs) to be introduced in the early 1990s. Subsequently, miglitol and voglibose have also been added to the list of AGIs available for clinical use.

Finally, study of the entero-insular axis and incretin hormones resulted in the discovery of two classes of antidiabetic agents—the glucagons-like peptide 1 (GLP-1) analogues, exenatide and liraglutide and the dipeptidyl peptidase IV (DPP-IV) inhibitors, sitagliptin and vildagliptin. These drugs are the latest additions to our antidiabetic armamentarium over the past couple of years.

### CLASSES OF OADs

Based on their primary mechanism of action, the various OADs can be grouped into 4 major categories:

1. Insulin secretagogues
2. Insulin sensitizers
3. Inhibitors of intestinal carbohydrate metabolism
4. Agents targeting the entero-insular axis and the incretins.

A list of drugs currently used or in development for the management of hyperglycaemia in type 2 DM is given in Table I.

### INSULIN SECRETAGOGUES

These agents directly stimulate insulin secretion from the cells of the pancreas. They include the sulphonylureas and the non-sulphonylureas.

#### *Sulphonylureas*

As a group, sulphonylureas have been classified as first-generation

TABLE I. Currently used antidiabetic agents

Class of antidiabetic agent	Specific agents	Mechanism of action	Percentage reduction in HbA1c
<i>Secretagogues</i>			
Sulphonylurea	Glibenclamide, gliclazide, glimepiride	Stimulate insulin secretion from $\beta$ cells of pancreas	1.5
Non-sulphonylurea (glinides)	Repaglinide, nateglinide	Stimulate insulin secretion from $\beta$ cells of pancreas	1–1.5
<i>Biguanide</i>	Metformin	Decrease hepatic glucose output, increase insulin sensitivity	1.5
<i>Thiazolidinedione</i>	Pioglitazone, rosiglitazone	PPAR agonists, increase insulin sensitivity	0.8–1.0
<i><math>\alpha</math>-glucosidase inhibitors</i>	Acarbose, miglitol, voglibose	Decrease and delay intestinal carbohydrate absorption	0.5–0.8
<i>GLP-1 analogues</i>	Exenatide, liraglutide	Stimulate glucose-induced insulin secretion	0.6
<i>DPP IV inhibitors</i>	Sitagliptin, vildagliptin	Prevent degradation of endogenous GLP-1, thus stimulate glucose-induced insulin secretion	0.5–0.9

PPAR peroxisome proliferator-activated receptor    GLP-1 glucagons-like peptide 1    DPP dipeptidyl peptidase

(chlorpropamide, tolbutamide, tolazamide, acetohexamide) and second-generation (glibenclamide, glipizide, gliclazide and glimepiride) agents based on their sequence of discovery. Currently, only second-generation agents are in clinical use, and are 20–50 times more potent than first-generation sulphonylureas on mg per mg basis. However, with the cloning of the constituents of the receptor for sulphonylureas, SUR 1 and Kir 6.2, better knowledge of their action is available, enabling their classification as cell selective and non-selective sulphonylureas. Further, based on their structure, sulphonylureas can be classified as:

1. Those containing sulphonylurea group, e.g. gliclazide, chlorpropamide and tolbutamide.
2. Those containing sulphonylurea and benzamido group, e.g. glibenclamide, glipizide and glimepiride.

**Mechanism of action.** Sulphonylureas bind to the SUR subunit of  $K^+$ -ATP channels on the cell of islet of Langerhans leading to closure of the  $K^+$  channel. This causes membrane depolarization followed by opening of calcium channels with influx of  $Ca^{2+}$  into the cell. Intracellular calcium mobilizes insulin-containing granules with release of insulin to the exterior. They augment both first and second phase of insulin secretion in a glucose-dependent and independent manner. The newer agents, especially glimepiride and gliclazide, are believed to have additional extra-pancreatic actions responsible for their antihyperglycaemic effects.

**Properties.** All the agents are well absorbed orally and reach peak plasma concentration in 2–4 hours. The onset of action in descending order is glipizide (fastest) followed by glimepiride, gliclazide and glibenclamide (slowest). However, this is not of much use in long term therapy. All are highly (90%–99%) bound to plasma proteins leading to important drug interactions responsible for hypoglycaemia. All are metabolized by the liver, with metabolites varying in their activity and route of excretion. The metabolites of glibenclamide, i.e. metaglinides are active while those of glipizide and gliclazide are inactive. The duration of action depends on the rate of metabolism, activity of metabolites and rate of excretion. Salicylates, warfarin, clofibrate and allopurinol enhance the likelihood of hypoglycaemia.

The average and maximum reduction in plasma glucose with all the commonly used agents is similar, with monotherapy causing a reduction in HbA1c by 1%–2%. The blood glucose-lowering effect starts plateauing after the half-maximal recommended dose is reached. The effectiveness of these agents depends on adequate cell function and decreases with the course of disease. Secondary failure of OADs is a reflection of the

progression of disease and not loss of sulphonylurea action *per se*.

Hypoglycaemia, the most common and life-threatening complication of sulphonylurea therapy, is due to non-physiological insulin secretion by sulphonylureas. Irregular eating habits, ageing, drug interactions and metabolic abnormalities such as renal failure (serum creatinine  $>2.5$  mg/dl) may aggravate it. Minor hypoglycaemia not requiring assistance is seen in 20% of sulphonylurea users annually and may necessitate a change in dose or agent while looking out for aggravating factors. Severe hypoglycaemia is usually seen with more potent and longer acting agents and occurs in 1% of sulphonylurea users annually. Among the agents in current use, severe hypoglycaemia occurs most commonly with glibenclamide and less frequently with gliclazide, glipizide and glimepiride. Severe hypoglycaemia due to sulphonylureas must be treated with hospitalization and intravenous glucose, taking care that initial recovery can be followed by recurrence of hypoglycaemia due to the long duration of action of the incriminating agent.

While weight gain is seen with all agents, glimepiride has been reported to be the most weight-neutral sulphonylurea. The average weight gain is 1–4 kg and it stabilizes in around 6 months. Other adverse events include hypersensitivity reactions, fever, jaundice, blood dyscrasias, acute porphyria in predisposed individuals and gastrointestinal disturbances.

The actions of non-selective sulphonylureas on vascular and cardiac muscle channels have been a matter of concern. Tolbutamide and glibenclamide have been shown to inhibit ischaemic preconditioning, a protective mechanism in the presence of chronic ischaemia of the myocardium. Glimepiride and probably gliclazide are safe on this count. Table II lists the characteristics of the commonly used sulphonylureas.

Intensive therapy with sulphonylureas results in a reduced risk of microvascular complications and a trend to decreasing macrovascular, including cardiovascular, complications. These agents are approved for use as monotherapy and in combination with insulin and all other oral agents except non-sulphonylureas.

#### *Non-sulphonylureas*

Currently two agents are available for clinical use—repaglinide (benzoic acid derivative) and nateglinide (phenylalanine derivative). They primarily reduce postprandial hyperglycaemia and are also called prandial insulin secretagogues.

**Mechanism of action.** Repaglinide stimulates insulin secretion from  $\beta$  cells by binding at a site distinct from the sulphonylurea-binding site. It only augments glucose-dependent insulin secretion

TABLE II. Characteristics of sulphonylureas in current clinical use

Agent	Daily dose (mg)	Half-life (hours)	Duration of action (hours)	Daily dose frequency	Activity of metabolites	Main route of excretion
Glibenclamide	2.5–20	12	12–24	Once/twice	Active	Bile ~50%
Glipizide	2.5–40	2–4	12–24	Once/twice	Inactive	Urine ~70%
Gliclazide	40–320	12	12–24	Twice	Inactive	Urine ~65%
Glimepiride	1–8	5–9	24	Once	Active	Urine ~80%

in the first phase and early second phase, i.e. short duration of action. Nateglinide binds to the SUR at the same binding site as for sulphonylureas, albeit transiently. It is specific for SUR 1 and mainly augments the glucose-dependent first phase of insulin secretion. Further, it has a minimal stimulatory effect when taken in the fasting state. The consequences of these differences in their metabolic actions compared with sulphonylureas are:

1. Better attenuation of postprandial glucose excursions
2. Reduced likelihood of hypoglycaemia in the late postprandial stage.

*Properties.* The major features of the two drugs are summarized in Table III.

TABLE III. Major features of non-sulphonylurea insulin secretagogues

Characteristic	Repaglinide	Nateglinide
Peak plasma concentration	1 hour	1 hour
Plasma half-life	1 hour	1.5 hours
Duration of action	Up to 5–8 hours	<4 hours
HbA1c reduction	1%–2%	0.5%–1%
Daily dose	0.5–4 mg with each meal	60–120 mg with each meal
Adverse effects	Hypoglycaemia and weight gain uncommon	Hypoglycaemia rare

These drugs are taken just before or with a meal. The drug is avoided if a meal is skipped. They are mainly useful in postprandial blood glucose control. They are useful in elderly and those with irregular eating patterns. They can be used in patients with moderate renal impairment but not with hepatic failure. The anti-hyperglycaemic effectiveness of repaglinide is comparable to that of sulphonylureas, while nateglinide is less efficacious.

These agents have not specifically been assessed for their long term efficacy in reducing micro- or macrovascular complications. They have been approved for monotherapy or in combination with metformin.

## INSULIN SENSITIZERS

Insulin resistance, at the level of liver, adipose tissue and skeletal muscle, plays a major role in the pathophysiology of type 2 DM. Biguanides and thiazolidinediones are the currently used insulin sensitizers.

### *Biguanides*

Metformin is the only agent approved for use in this category, since phenformin was banned due to an excess risk of lactic acidosis.

*Mechanism of action.* Metformin activates adenosine monophosphate-activated protein kinase (AMPK) resulting in decreased hepatic gluconeogenesis, glycogenolysis and lipogenesis with increased fatty acid oxidation. The net result of this is decreased hepatic glucose output along with increased hepatic insulin sensitivity. Metformin has also been shown to increase

peripheral glucose disposal, though this effect may be mediated by reduced glucotoxicity and not through a direct drug effect. It does not cause any stimulation of insulin secretion.

*Properties.* Metformin is absorbed rapidly after oral administration. It does not bind to plasma proteins and it is not metabolized. It has a plasma half-life ( $t_{1/2}$ ) of 2–5 hours. It is excreted unchanged in urine mainly by tubular secretion. Cimetidine may interfere with this process. More than 90% of the absorbed drug is excreted in 12 hours.

The beneficial effects of metformin include weight loss besides improvement in glycaemia. In placebo-controlled trials, metformin monotherapy reduces HbA1c by 1%–2%, similar to that reported with sulphonylureas. This has also been confirmed in head-to-head comparisons between sulphonylureas and metformin. Improvement in lipid profile (reduced low density lipoprotein cholesterol and triglycerides) and plasminogen activator inhibitor (PAI)-1 levels has also been described with metformin. Reports also suggest a reduction in vascular reactivity, which, in conjunction with lowered circulating insulin levels, possibly contributes to the cardiovascular benefits attributed to metformin therapy.

Acute gastrointestinal side-effects including anorexia, metallic taste, abdominal discomfort, bloating and diarrhoea are seen in 10%–20% of patients. This may be due to decreased intestinal glucose absorption by metformin. It can be reduced by starting the drug in low doses and slowly increasing the dose. Around 5%–10% of patients cannot tolerate the drug and require its discontinuation. Chronic use decreases intestinal vitamin B<sub>12</sub> and folate absorption.

Lactic acidosis is the most dreaded complication though the likelihood is 100 times less than that with phenformin. Contraindications and precautions to use of metformin include:

1. Moderate-to-severe renal failure: Serum creatinine  $\geq$  1.4 mg/dl in women and 1.5 mg/dl in men.
2. Previous history of lactic acidosis.
3. Gastrointestinal disorders and alcohol abuse.
4. Other conditions predisposing to lactic acidosis: hepatic disease, cardiac failure, chronic hypoxic lung disease.
5. It should be stopped 48 hours before the administration of intravenous contrast media or a surgical procedure and restarted later, not earlier than 48 hours, after renal functions are confirmed to be normal.
6. Metformin should also be stopped immediately in the presence of any acute illness predisposing to tissue hypoxia. A very low calorie diet or fast mandates stoppage of metformin.

If these precautions and contraindications are observed, the likelihood of lactic acidosis is nearly abolished.

Metformin is used in daily doses of 500–2500 mg. Sustained release preparations of metformin for once daily use are also available.

Intensive therapy with metformin has been shown to reduce the incidence of micro- and macrovascular complications. A significant reduction in the risk of cardiovascular events, not reported for

intensive therapy with sulphonylureas, has been reported with metformin therapy. These agents are approved for use as monotherapy and in combination with insulin and all other oral agents.

#### *Thiazolidinediones*

These agents reduce insulin resistance at skeletal muscle and adipose tissue. Pioglitazone and rosiglitazone are the two agents in clinical use. Troglitazone, an earlier thiazolidinedione, was removed from the market due to a rare idiosyncratic hepatocellular injury.

**Mechanism of action.** They act by stimulation of PPAR $\alpha$ , a nuclear receptor expressed predominantly in adipose tissue and to a lesser extent in liver and muscle. Thiazolidinediones promote differentiation of pre-adipocyte to adipocyte with accompanying lipogenesis, increase glucose transporter (GLUT-4) expression in adipose tissue leading to increased glucose uptake and promote shift of fat from visceral to subcutaneous depots. Thiazolidinediones also decrease tumour necrosis factor and increase adiponectin production by adipocytes, thereby contributing to the increase in insulin sensitivity and decrease in plasma glucose. Recent evidence suggests that thiazolidinediones also reduce cell apoptosis and preserve cell function. Similar to biguanides, these agents do not act as insulin secretagogues.

**Properties.** Both agents are rapidly and completely absorbed with peak plasma levels achieved within 2 hours. Absorption is delayed by food. The metabolites of pioglitazone are active and excreted in bile while those of rosiglitazone are weakly active and are excreted in urine. Other metabolic actions reported for thiazolidinediones include reduction in urinary albumin excretion, blood pressure and PAI-1 level. Rosiglitazone increases total cholesterol by increasing low density and high density lipoprotein cholesterol, while pioglitazone decreases triglyceride levels. Reduction in blood pressure, increased fibrinolysis and improved endothelial function has also been documented with the use of thiazolidinediones, though the clinical relevance of these observations is yet unclear.

Used as monotherapy, thiazolidinediones decrease HbA1c by 1%–2%, a range similar to that seen with sulphonylurea and metformin therapy. Head-to-head studies with metformin and sulphonylureas have confirmed that the anti-hyperglycaemic efficacy of these agents is similar.

Adverse effects include weight gain of around 1–4 kg due to a combination of increased peripheral fat and fluid retention; this stabilizes in 6–12 months. Fluid retention causing peripheral oedema, pulmonary oedema and congestive cardiac failure are major concerns with thiazolidinediones. Peripheral oedema occurs in 3%–5% of patients using thiazolidinediones as monotherapy. Congestive cardiac failure is reported in 1% of cases with monotherapy and in 2%–3% of cases on combination therapy. Fluid retention can cause dilutional anaemia. The initial concern about the potential hepatotoxicity of the currently marketed agents has abated, and the advisory regarding mandatory periodic liver function testing has been withdrawn. The contraindications and caution for therapy with thiazolidinediones include:

1. Congestive heart failure: New York Heart Association (NYHA) classes II, III and IV.
2. Liver dysfunction with transaminase levels >2.5 times upper limit of normal.
3. Caution is needed in patients with mild renal failure and anaemia in view of fluid retention. Haemoglobin should be checked before starting thiazolidinediones.

**Recent concerns.** A recent meta-analysis has suggested that patients on rosiglitazone have a 43% excess risk of myocardial infarction and 64% excess risk of cardiovascular death. A recent interim analysis showed a non-significant increase in hospitalization and death from cardiovascular causes, which has not alleviated the concerns raised by the meta-analysis. A similar meta-analysis indicates that, unlike rosiglitazone, pioglitazone is not associated with any excess cardiovascular risk, and may even be protective. In response, the US Food and Drug Administration (FDA) will probably advise thiazolidinedione manufacturers to carry a warning with details of increased cardiovascular risk while marketing these agents. Recent evidence also suggests that both agents reduce bone mineral density and pose an increased risk of fractures in post-menopausal women.

Pioglitazone is started at a dose of 15 mg once a day and increased to a maximum of 45 mg once a day. Rosiglitazone is started at 2–4 mg once a day and increased to 8 mg/day in 1 or 2 divided doses. Its full effect is seen in 2–3 months. The long term efficacy of these agents in reducing diabetic complications has not been proven in clinical trials. Thiazolidinediones can be used as monotherapy, and also in combination with secretagogues and insulin sensitizers. Combination with insulin should be prescribed with caution due to the increased risk of weight gain and fluid retention.

## INHIBITORS OF INTESTINAL CARBOHYDRATE METABOLISM

### *$\alpha$ -glucosidase inhibitors (AGIs)*

The agents in clinical use are acarbose, miglitol and voglibose.

**Mechanism of action.**  $\alpha$ -glucosidases are enzymes involved in the breakdown of complex carbohydrates to monosaccharides for absorption in the jejunum. They include maltase, isomaltase, dextranase, glucoamylase and sucrase expressed in the brush border of the enterocytes lining the intestinal villi. AGIs are competitive, reversible inhibitors of these enzymes that prevent breakdown of oligosaccharides and disaccharides to monosaccharides. This retards the rate of carbohydrate digestion, delaying and decreasing the rise in postprandial plasma glucose. The affinity of acarbose for sucrase is  $10^5$  more than that of sucrose. In addition, AGIs inhibit pancreatic amylase and are also known to increase secretion of GLP-1, cholecystokinin and peptide YY, thereby reducing gastric motility and increasing satiety. There is no effect on intestinal glucose absorption as also glucose or glycogen metabolism.

**Properties.** Acarbose acts in the intestine locally, and is degraded by amylase and intestinal bacteria. Some degradation products are absorbed and excreted in urine over 24 hours.

Miglitol is significantly absorbed in the upper small intestine after oral use. It is neither bound to plasma proteins nor metabolized in the body. Around 60% is excreted via kidneys and 30% in the faeces. Voglibose is poorly absorbed after oral doses.

The major metabolic effects include reduction in the postprandial rise in plasma glucose by 30–50 mg/dl and triglycerides to a small degree. There is also secondary decrease in fasting plasma glucose to a small degree. Used as monotherapy, AGIs decrease HbA1c by 0.5%–1%. Efficacy does not decrease with advancement of disease.

Gastrointestinal symptoms such as flatulence, abdominal discomfort or pain and loose stools are common with the use of AGIs. As undigested carbohydrates reach the colon, they are fermented by colonic bacteria, with the resultant gas-causing symptoms. Starting the drug at a low dose and then

its slow increase decreases the symptoms in all but 20%–30% of patients.

Used as monotherapy, hypoglycaemia is not a concern. However, AGIs can potentiate hypoglycaemia caused by other agents. In such cases, glucose and not sucrose should be the agent of choice for oral use so that enzyme inhibition is bypassed. Voglibose can be used in patients with mild-to-moderate renal failure and hepatic impairment.

The contraindications and caution for the use of AGIs include:

1. AGIs are contraindicated in chronic intestinal diseases such as irritable bowel syndrome, inflammatory bowel disease and others where gaseous distension can aggravate symptoms.
2. Severe renal and liver failure.
3. Pregnancy and lactation.

With AGIs, one has to ensure dietary compliance with no simple sugars and more of complex carbohydrates. The drug is taken with the first bite of the meal so that it remains in the intestine during digestion of food. Table IV lists some salient features of AGIs.

#### AGENTS TARGETING THE ENTERO-INSULAR AXIS AND THE INCRETINS

These agents are not yet available for clinical use in India. The presence of an entero-insular axis was made apparent by the fact that using equivalent glucose loads, oral glucose tolerance tests resulted in a higher insulin peak than the intravenous glucose tolerance test. Gut hormones contributing to incremental insulin release were called 'incretins'. GLP-1 is the major incretin and is secreted by the ileum and, to some extent the colon, with levels rising within 15 minutes of ingesting a meal. Following ingestion of a meal, GLP-1 levels increase within 15 minutes. It has a half-life of 1–2 minutes as it is degraded by DPP IV to GLP-1 (9–36) amide. The GLP-1 receptor is expressed on pancreatic cells, lung, brain, liver, skeletal muscle and adipose tissue among others. The actions of GLP-1 include:

1. Insulinotropic actions: GLP-1 stimulates glucose-dependent insulin secretion; with euglycaemia there is no stimulation.
2. Glucagonostatic effect: suppresses glucagon secretion in a glucose-dependent manner.
3. Proliferative and anti-apoptotic effect: GLP-1 may stimulate proliferation and neogenesis of cells while inhibiting apoptosis.
4. On gastrointestinal tract: GLP-1 inhibits gastric emptying thereby delaying postprandial plasma glucose rise and also causing satiety.
5. On central nervous system: GLP-1 promotes satiety and weight loss.

Impaired glucose tolerance and type 2 DM are characterized by low levels of GLP-1 with normal sensitivity. Clinical use of GLP-1 needs continuous infusion as it is rapidly degraded. This is overcome using enzyme resistant analogues (Exendin 4, Liraglutide) or with DPP IV inhibitors (sitagliptin and

vildagliptin). Preclinical studies suggest that these agents may also promote cell neogenesis and proliferation.

#### GLP-1 receptor agonists (Incretin mimetics)

*Exendin 4 (Exenatide)*. It is obtained from the saliva of the Gila monster, *Heloderma suspectum*. Synthetic exendin 4 is also available. It is resistant to DPP IV and following subcutaneous injection has a plasma half-life of about 26 minutes. The usual dose is 5–10 µg subcutaneously taken twice a day, up to 60 minutes before each meal. Nausea and vomiting may be related to delayed gastric emptying or central effects. It can be used in combination with sulphonylureas, metformin or thiazolidinediones, and the dose of sulphonylureas may need to be reduced if hypoglycaemic symptoms appear. With exenatide therapy, patients may report a reduction in appetite and most of them also have weight loss. Exenatide has only recently become available in India and its precise place in the management of type 2 diabetes in India is still to be established.

Liraglutide, a synthetic GLP-1 analogue, has an acyl side chain attached that results in non-covalent binding to albumin. The half-life is about 15 hours allowing once daily injection. The dose is up to 2 mg/day. This agent also suppresses glucagons, reduces fasting blood glucose and causes weight loss.

#### DPP IV inhibitors

Sitagliptin and vildagliptin, both inhibit DPP IV activity by 100% within 15–30 minutes of their oral ingestion, and more than 80% inhibition lasts for 16 hours or more. This allows both agents to be given as a once daily dose of 100 mg. While sitagliptin has received FDA approval, vildagliptin is awaiting regulatory approval.

*Sitagliptin*. Monotherapy with once daily dose results in a reduction in HbA1c by 0.8%–1%, and is associated with either weight neutrality or weight loss. This agent has also been studied in combination therapy with metformin and thiazolidinediones and leads to an additional decline in HbA1c of approximately 0.75%. A concern with use of DPP IV inhibitors is that these agents may also cleave other bioactive molecules involved in the immunoinflammatory pathway. This has not been borne out by clinical studies till date. Current data suggest that DPP IV inhibitors are best positioned as therapy early in the course of type 2 DM either as monotherapy or in combination with metformin and thiazolidinediones.

#### USES OF OADs

Diet, exercise and weight loss are the key non-pharmacological interventions for the management of type 2 DM (details provided in an earlier article in the series). Over a period of time, these lifestyle interventions alone are not adequate to attain optimal glycaemic control, necessitating the introduction of OADs. However, it must be emphasized that continuing lifestyle modification is a critical requirement to ensure target blood glucose levels and ameliorate cardiovascular risk factors even

TABLE IV. Salient features of  $\alpha$ -glucosidase inhibitors

Characteristic	Acarbose	Miglitol	Voglibose
Intestinal absorption	1%–2%	Significant	Minimal
Gastrointestinal symptoms	Significant	Moderate	Least
Dose	Start with 25–50 mg with each meal; increase to 50–100 mg with each meal	Start with 25 mg with each meal; increase to 50–100 mg with each meal	Start with 0.2 mg with each meal; increase to 0.3 mg with each meal

when the patient is concurrently on pharmacological therapy.

#### *OAD monotherapy*

How does a physician choose the most appropriate agent for monotherapy for a particular patient? The preceding discussion makes it clear that except for AGI, nateglinide and the newer agents, all other drugs currently in clinical use cause comparable reduction in HbA1c. Table V provides a synopsis of the relative merits and concerns for individual agents.

Recent guidelines from the American Diabetes Association and European Association for the Study of Diabetes, recommend metformin to be the best first-line agent, especially in obese patients, because of the weight loss/weight neutrality associated with this agent. The long term benefits in reducing micro- and macrovascular complications as demonstrated by the UKPDS and the near absence of hypoglycaemia make this drug an attractive choice for initiating pharmacotherapy.

Insulin secretagogues are currently preferred less than metformin while starting monotherapy because of the concern regarding weight gain and hypoglycaemia. Additional unresolved issues are the possible adverse cardiovascular implications of hyperglycaemia. However, they remain an important part of combination treatment. They are also appropriate for monotherapy if fasting blood glucose levels are high (about 250–300 mg/dl) and in non-obese patients. Like metformin therapy, long term therapy with these agents has been associated with reduction in microvascular complications, though benefits with regards to macrovascular complications are equivocal.

Non-insulin secretagogues are best considered as 'niche' agents, to be used in special situations, e.g. patients with irregular meal timings. They do not provide any advantage over conventional sulphonylureas, other than shorter duration of action. While this results in better postprandial control it may be associated with preprandial hyperglycaemia.

Thiazolidinediones are an important group of insulin sensitizers for whom the entire spectrum of metabolic effects and side-effects still need to be elucidated. They are slow in

onset of action taking up to 8–12 weeks to manifest their full hypoglycaemic effect. This makes them less attractive if the patient has symptomatic hyper-glycaemia and needs prompt reduction in blood glucose. Similarly, the significant weight gain and fluid retention with resultant pedal oedema and likelihood of precipitating congestive cardiac failure remain a matter of concern. The recent literature suggesting an excess risk of cardiovascular events and mortality also needs to be resolved. At present, there is limited evidence to strongly recommend thiazolidinediones as first-line agents for monotherapy.

In summary, while there may be no compelling reason to recommend any one group of agents, metformin is possibly the most appropriate drug for monotherapy especially in the overweight patient. Patient factors such as age, weight, co-morbid conditions, regularity of meals and interaction with other medication must be considered before making a decision.

#### *Combination therapy*

Since a combination of insulin deficiency and insulin resistance are responsible for type 2 DM, combination therapy with insulin sensitizers and insulin secretagogues becomes logical, especially as the disease progresses. The most commonly prescribed combination is metformin and sulphonylurea, though sulphonylurea with thiazolidinediones and metformin with thiazolidinediones have their proponents in specific clinical situations. There is no evidence to show that given a comparable reduction in HbA1c, any one combination is superior to the other, underlining the primacy of glycaemic control and not the means to attain target blood glucose levels.

When a two-drug combination is not adequate to meet glycaemic targets, triple drug combination (sulphonylurea, metformin and thiazolidinediones) can be considered. Data suggest that adding a third drug to a 2-drug combination is unlikely to reduce the HbA1c by more than 1%. The inference thereby is that if HbA1c exceeds the target for control by >1% while on optimal doses of 2 agents, adding a third drug is unlikely to help achieve the target; and it may be advisable to consider insulin therapy at this juncture.

TABLE V. Currently available oral hypoglycaemic agents for type 2 diabetes mellitus

Sulphonylureas	Non-sulphonylureas	Metformin	$\alpha$ -glucosidase inhibitors	Thiazolidinediones
<i>Mechanism of action</i>				
Increased pancreatic insulin secretion	Increased pancreatic insulin secretion	Reduced hepatic glucose output	Decreased carbohydrate absorption	Increased peripheral glucose disposal
<i>Advantages</i>				
Well established Reduce microvascular complications	Target postprandial hyperglycaemia Possibly less hypoglycaemia	Well established Weight loss No hypoglycaemia Reduce micro- and macro-vascular complications	Targets postprandial hypoglycaemia No hypoglycaemia	No hypoglycaemia Possible non-glycaemic benefits Possible $\beta$ cell preservation
<i>Disadvantages</i>				
Hypoglycaemia Weight gain	Multiple dosing Hypoglycaemia Weight gain	Adverse gastrointestinal effects Several contraindications; precautions for use Lactic acidosis (rare)	Multiple dosing Adverse gastrointestinal effects	Weight gain Oedema Slow onset of action Recent concerns regarding cardiovascular risk
<i>Recommendations for use</i>				
Monotherapy Combination with metformin, thiazolidinediones, $\alpha$ -glucosidase inhibitors and insulin	Monotherapy Combination with metformin	Monotherapy Combination with insulin, sulphonylurea, non-sulphonylureas and thiazolidinediones	Monotherapy Combination with sulphonylurea	Monotherapy Combination with insulin, sulphonylurea and metformin

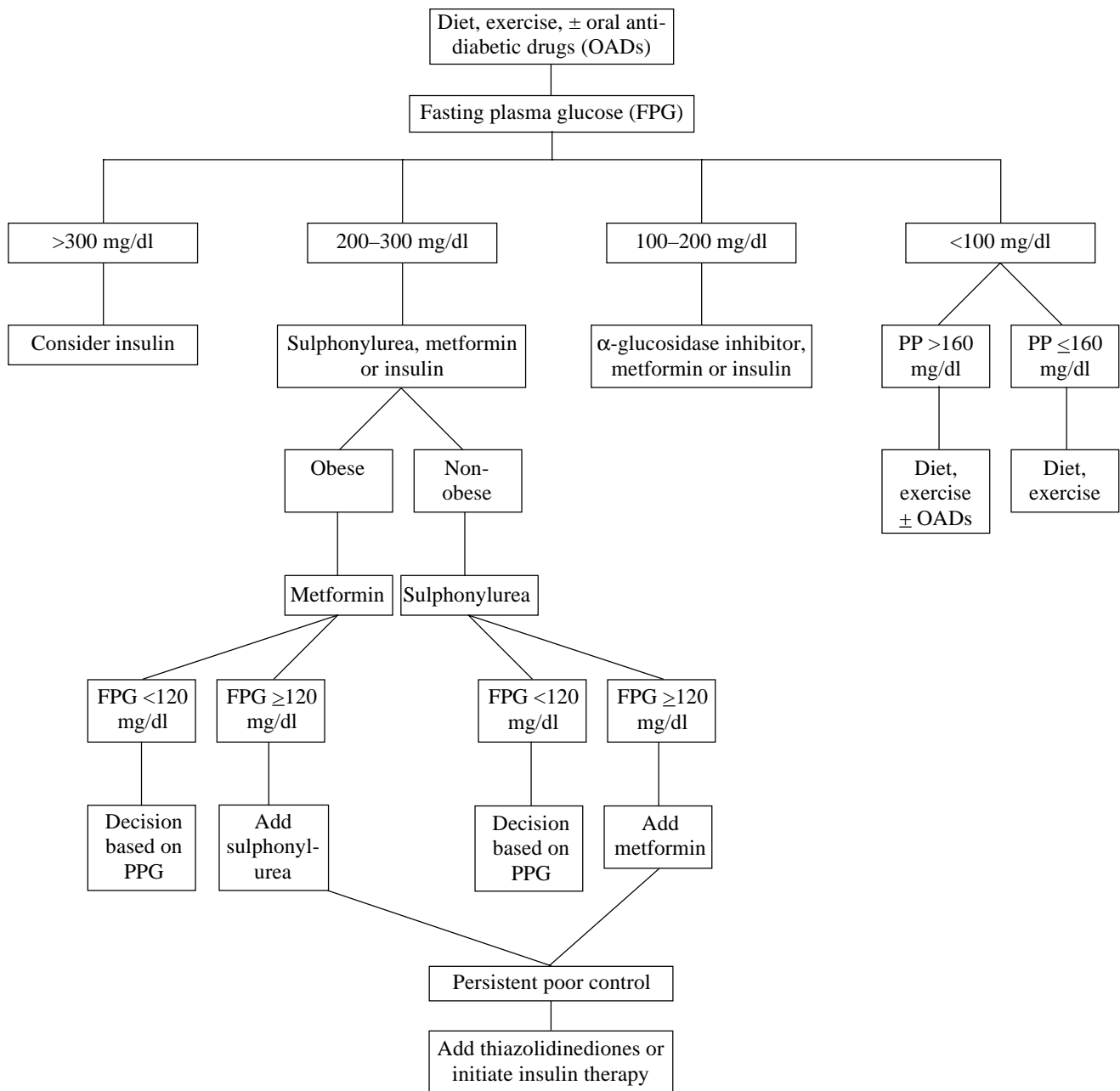


FIG 1. Suggested approach to the use of drug therapy to attain glycaemic control in patients with type 2 diabetes mellitus  
PP post prandial

Two to three monthly HbA1c monitoring is required to guide therapy and decide regarding dose escalation, introduction of additional agents or initiating insulin therapy. The target for HbA1c remains 6.5%–7% depending on the age and co-morbid conditions of the individual patient.

A flow chart for the management of blood glucose in patients with type 2 DM is shown in Fig. 1.

#### CONCLUSIONS

Lifestyle modifications provide the cornerstone for metabolic control of patients with type 2 DM. However, with the passage of time, these alone are inadequate to attain glycaemic targets and antihyperglycaemic pharmacotherapy needs to be introduced. The main pathophysiological events in type 2 DM which are

targeted by drug treatment are insulin deficiency and insulin resistance. Metformin, an insulin sensitizer is the preferred agent for monotherapy in obese patients with type 2 DM, while sulphonylureas are the key agents for non-obese patients. Thiazolidinediones are insulin sensitizers which play an important role in combination therapy, though recent concerns about potential cardiovascular risks need to be addressed before their precise place in the therapeutic armamentarium can be unequivocally assigned. In the event that glycaemic control is not achieved by monotherapy, 2- and 3-drug combinations can be used.

#### SUGGESTED READING

1 Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes. *JAMA* 2002;287: 360–72.