

Current Therapeutic Strategies for Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus is now regarded a worldwide epidemic with diabetes-related complications exacting a heavy toll on those with poor metabolic control. Although there is no cure currently, the therapeutic armamentarium has expanded over the last few years to five classes of oral agents – sulfonylureas, biguanides, meglitinides, thiazolidinediones and alpha-glucosidase inhibitors. Sulfonylureas continue to be the mainstay oral hypoglycaemic agents for type 2 diabetics because they are potent insulin secretagogues and cost-effective. Metformin exerts its main effect by reducing hepatic glucose output and is proven to particularly benefit obese type 2 diabetics. Meglitinides are rapid-acting insulin secretagogues targeting at postprandial hyperglycaemia and this class of drug is useful for those who are at risk of hypoglycaemia with longer-acting sulfonylurea drugs. Thiazolidinediones constitute a new class of insulin sensitizers that work predominantly in improving glucose uptake by the adipose tissues and skeletal muscles. Alpha-glucosidase inhibitors delay the digestion and absorption of polysaccharides, thus attenuating postprandial hyperglycaemia. This review article briefly examines the nature of these oral agents, including the role of combination therapy and insulin where clinically indicated.

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Key words: Diabetes mellitus, Drug therapy, Insulin, Insulin analogues, Oral hypoglycaemic agents

Introduction

Type 2 diabetes mellitus is now recognised as a metabolic syndrome and although the treatment paradigm has shifted from one that focuses solely on glycaemic control to one addressing global cardiovascular risk factors in a particular individual, glycaemic control remains one of the key challenges that the physician faces in his daily practice.¹ The practicing physician must be familiar with the basic pharmacology of the various classes of hypoglycaemic drugs to ensure its effective and rational use. This is becoming an increasingly complicated task given the rapid pace of progress in diabetes therapy. There is also a need to appreciate the pathophysiology of type 2 diabetes and the concept of insulin resistance and β -cell dysfunction, and how this may influence the choice of therapeutic agents in any particular patient. This review summarises the major drug classes and provides evidence-based approach in the management of type 2 diabetes.

The Burden of Type 2 Diabetes Mellitus

Type 2 diabetes is still not satisfactorily managed

anywhere in the world, thereby accounting for the considerable morbidity and mortality from diabetes-related complications. Epidemiologically, the Asia-Pacific region alone accounts for nearly 50% of the world's diabetic patients, 95% or more being type 2 diabetics.² Singapore has one of the highest prevalence of diabetes in the region. The National Health Survey of Singapore in 1998 estimated an overall prevalence of 9.0% among adults 18 to 69 years of age, with rates highest among Indians (15.8%) and Malays (11.3%). Diabetes alone is the sixth commonest cause of death, excluding deaths secondary to cardiovascular and renal complications.³

Relevance of Basic Pathophysiology of Type 2 Diabetes

Patients with type 2 diabetes mellitus have coexistent problems of insulin resistance and β -cell dysfunction, although to varying degrees. This may range from predominantly insulin resistance with relative insulin deficiency to predominantly insulin secretory defect with insulin resistance.⁴ In type 2 diabetes, insulin resistance plays a pivotal role in the pathogenesis of hyperglycaemia

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by reducing insulin-mediated glucose uptake and disposal in adipose tissues and skeletal muscles. Insulin resistance also leads to accentuated gluconeogenesis and hepatic glucose output in the liver. Insulin resistance is initially offset by hyperinsulinaemia, an adaptive counter-response of the pancreatic β -cells. However, this will ultimately lead to impaired β -cell secretory function and progressive insulinopaenia.⁵ Any pharmacologic intervention must therefore address these two related aspects adequately to be successful and effective.

Guidelines, Targets and End-points

The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have conclusively proven that intensive blood glucose control significantly decreases the risk of microvascular disease in both type 1 and type 2 diabetic patients respectively.^{6,7} These studies revealed that a 1% reduction in HbA1c translates into a 35% to 60% risk reduction for microangiopathy. Therefore, the glycaemic targets for patients with type 2 diabetes are not different from those patients with type 1 diabetes.

The targets of glycaemic control may be defined as 'ideal', 'optimal', 'suboptimal', and 'unacceptable', depending on the range of HbA1c and the respective pre-meal and 2-hour post-meal capillary blood glucose values (Table I). The American Diabetes Association (ADA) has recommended that action be taken when the fasting plasma glucose exceeds 7.8 mmol/L (140 mg/dL) and HbA1c exceeds 8%. The goals are a fasting glucose less than 6.7 mmol/L (120 mg/dL) and HbA1c below 7%.⁸ These targets should serve as general guidelines and the actual therapeutic goal should be individualised based on clinical variables such as age, renal function and other co-morbidities that may predispose an individual to hypoglycaemia.

Oral Pharmacotherapeutic Options

Table II summarises the classes of oral antidiabetic agents currently available for the treatment of type 2 diabetes. These are classified into sulfonylureas, meglitinides, biguanides, thiazolidinediones, and α -glucosidase inhibitors. Both sulfonylureas and meglitinides are insulin secretagogues; they work by stimulating the

pancreatic β -cell secretion of insulin. These are true oral hypoglycaemic agents because they can potentially induce hypoglycaemia even when used as monotherapy. Metformin and thiazolidinediones are insulin sensitisers as they decrease plasma glucose levels by enhancing the action of insulin *in vivo* without stimulating endogenous insulin secretion. Alpha-glucosidase inhibitors retard the rate of digestion of dietary carbohydrates and hence prolong the absorption of glucose from the gut. However, the final amount of glucose absorbed and intake of total calories from carbohydrates remains unchanged.

Sulfonylureas – Quest for the Next Generation and Beyond

Sulfonylureas are still one of the cornerstone classes of drugs for the treatment of type 2 diabetes mellitus. As insulin secretagogues, they bind to the sulfonylurea receptor (SUR1) closely coupled to the ATP-sensitive, inwardly rectifying potassium Kir6.2 channel, so-called K_{ATP} channel on the pancreatic β -cells. Under the normal resting state, the K_{ATP} channel opens with efflux of potassium. Activation of the SUR1 leads to closure of the K_{ATP} channel. By inhibiting the efflux of potassium, the β -cell membrane depolarises and opens the voltage-sensitive calcium channels. The intracellular calcium flux in turn leads to a series of vesicular trafficking that culminates in insulin secretion (Fig. 1).

The first-generation sulfonylureas, except for tolbutamide, have largely fallen out of favour due to significant adverse effects including protracted and refractory hypoglycaemia and the syndrome of

TABLE II: THE AVAILABLE TREATMENT OPTIONS FOR TYPE 2 DIABETES

Insulin secretagogues	- Sulfonylureas - Meglitinides
Insulin sensitisers	- Biguanides (metformin) - PPAR-γ agonists
Compounds that reduce the rate of glucose absorption	α-glucosidase inhibitors
Insulin therapy	Rapid-, intermediate- and long-acting recombinant human insulins and their analogues

TABLE I: TARGETS OF GLYCAEMIC CONTROL

	Ideal	Optimal	Suboptimal*	Unacceptable
Pre-meal glucose** (mmol/L)	4.0-6.0	6.1-8.0	8.1-10.0	>10.0
2h post-meal glucose** (mmol/L)	5.0-7.0	7.1-10.0	10.1-13.0	>13.0
HbA1c (%)	4.5-6.4	6.5-7.0	7.1-8.0	>8.0

* Adequate goal in geriatric patients and individuals with advanced diabetic complications or other co-morbidities

** Values refer to capillary blood sample

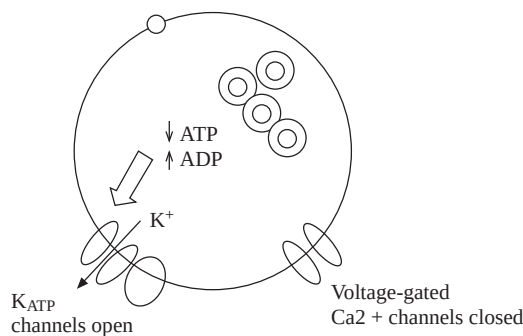


Fig. 1a. Resting state.

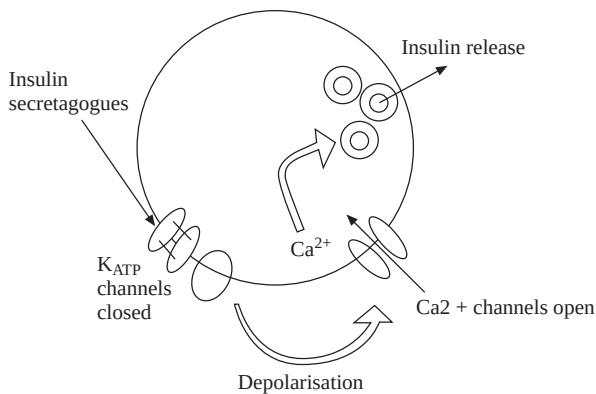


Fig. 1c. Insulin secretagogue-mediated insulin release

Fig. 1. Mechanisms of β -cell insulin secretion.

inappropriate anti-diuretic hormone (ADH) secretion (SIADH).⁹ The second-generation sulfonylureas (e.g. glibenclamide, glipizide, gliclazide) became available since the 1980s, and these agents generally have more acceptable side-effects profiles. However, hypoglycaemia remains an obligatory trade-off, especially with long-acting agents (e.g. glibenclamide) or short-acting drugs with active metabolites that have long half-lives (e.g. glipizide).¹⁰ Glimepiride is one of the latest additions to the sulfonylurea family and emerging clinical studies showed a lower risk of hypoglycaemia and less weight gain as compared to the older sulfonylureas.¹¹ The commonly used sulfonylureas and their dosing guide are summarised in Table III.

Increasing awareness of the differential tissue selectivity of sulfonylureas has led to recent interest in elucidating tissue selectivity of sulfonylureas specific for SUR1 of the pancreatic β -cells. This is because *in vitro* patch clamp studies showed that closure of the K_{ATP} channels in SUR2A of cardiac muscle cells and SUR2B of vascular smooth muscle cells, respectively, may lead to undesirable physiological consequences like worsening of tissue ischaemia.¹² Sulfonylurea compounds with both sulfonylurea and benzamido moieties (e.g. glibenclamide

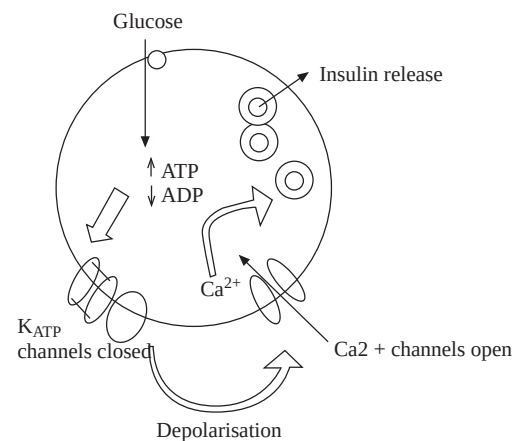


Fig. 1b. Glucose-mediated insulin release.

and glimepiride) bind to both SUR1 and SUR2A/SUR2B subtypes, whereas drugs with pure sulfonylurea moiety alone (e.g. tolbutamide, gliclazide) bind with high affinity only to the SUR1. However, the clinical significance of these tissue specificities remains to be established.

Meglitinides – The Prandial Glucose Regulators

The loss of the acute insulin response, otherwise called “first phase” insulin secretion, constitutes the basis of postprandial hyperglycaemia in type 2 diabetics. The meglitinides are developed to target at postprandial hyperglycaemia in a way similar to the use of rapidly acting insulin analogues before a meal.

Like sulfonylureas, meglitinides stimulate insulin secretion by closing the K_{ATP} channels on the membrane of the pancreatic β -cell via activation of the benzamido site on SUR1.¹³ Its unique pharmacokinetic profile of rapid absorption coupled with extensive hepatic biotransformation translates into a drug with rapid-onset and rapid-offset effect. This property makes it an ideal prandial glucose regulator, allowing greater flexibility in mealtimes to accommodate a wider range of eating habits. Preprandial dosing may reduce the risk of hypoglycaemia should a meal be missed, and forestall hyperglycaemic excursions when additional meals are consumed. When used as monotherapy, however, meglitinides may not provide adequate control of post-absorptive or fasting glycaemia.

The currently available meglitinides are repaglinide and nateglinide. For treatment naïve patients, the initial starting dose of repaglinide is 0.5 mg just prior to a meal. The dose recommended in those switching over from sulfonylureas is 1 mg before each main meal, with the maximum daily dose up to 16 mg. The usual starting dose of nateglinide is 120 mg before each meal (Table IV).

Reductions in HbA1c of up to 1% to 2% can be expected

TABLE III: SUMMARY OF THE COMMONLY USED SULFONYLUREAS FOR TYPE 2 DIABETES

Sulfonylureas					
	Starting dose	Maximum dose	Duration of action	Mean HbA1c reduction	Common adverse effects
Tolbutamide	250 mg bid	1000 mg tid	6-16 h	1% to 2 %	Hypoglycaemia Weight gain
Glibenclamide (Glyburide)	2.5-5 mg om	10 mg bid	24-38 h	Note: Although the mean efficacy of sulfonylureas average between 1% to 2% across the entire drug class, one can still switch to a more potent second-generation sulfonylurea when HbA1c fails to reach the desired target if the initial agent used was tolbutamide.	
Glipizide	5 mg om	20 mg bid	12-24 h		
Gliclazide/ Gliclazide MR	80 mg om or 30 mg om (MR)	160 mg bid or 120 mg om (MR)	10-12 h or 24 h (MR)		
Glimepiride	1-2 mg om	8 mg om	24 h		

MR: modified release preparation

TABLE IV: THE OTHER CLASSES OF ANTIDIABETIC AGENTS (NON-SULFONYLUREAS)

	Starting dose	Maximum dose	Duration of action	Mean HbA1c reduction	Common adverse effects
Meglitinides					
Repaglinide	0.5 mg bid-qid (with meals)	4 mg qid (with meals)	1-4 h	1-2%	Hypoglycaemia, weight gain
Nateglinide	60 mg tid (with meals)	120 mg tid (with meals)	1-4 h	1-2%	Hypoglycaemia, weight gain
Biguanides					
Metformin	250 mg bid-850 mg om	850 mg tid-1000 mg tid	1.7-4.5 h	1-2%	Anorexia, nausea, vomiting, flatulence, diarrhoea
Thiazolidinediones					
Rosiglitazone	4 mg om	8 mg om	24 h	1-1.5%	Anaemia (dilutional), fluid retention, weight gain
Alpha-glucosidase Inhibitors					
Acarbose	25 mg tid (with meals)	100 mg tid (with meals)	6 to 12 h	0.5-1%	Diarrhoea, abdominal pain, flatulence

of the meglitinides, an efficacy fairly similar to that of sulfonylureas. This group of agents can act synergistically in combination with metformin and thiazolidinediones. However, meglitinides are not useful in patients with primary or secondary failure to sulfonylureas. Meglitinides are generally safe and well tolerated; however, it is contraindicated in severe renal and hepatic failure, pregnancy and lactation. Weight gain may occur though this is generally less severe compared to sulfonylureas.

Biguanides—The Return of Metformin

Metformin has remained one of the most efficacious antidiabetic agents, despite the withdrawal of phenformin and buformin because of potential adverse effect of lactic acidosis. Metformin is hydrophilic and is eliminated rapidly by the kidneys; this dissimilarity leads to a significantly reduced risk of lactic acidosis estimated at 3 cases per 100,000 patient years.^{14,15}

Metformin reduces hyperglycaemia predominantly by reducing hepatic glucose output. This is achieved by inhibition of gluconeogenesis and to a lesser degree

glycogenolysis by the liver. Secondly, it also reduces hyperglycaemia by increased insulin-mediated glucose disposal at the adipose tissue and skeletal muscle through upregulation of glucose transporters.¹⁶ It can also interfere with glucose absorption from the small intestine and reduce postprandial glycaemic excursions. Besides improving glycaemic control, metformin leads to favourable reductions in serum triglycerides concentrations via decreases in very low density lipoprotein (VLDL) synthesis, as well as mild decrease in total cholesterol and slight increase in high density lipoprotein (HDL) levels.¹⁷ Because free fatty acid oxidation result in the accumulation of acetyl co-enzyme A and citrate, which in turn inhibit glycolytic enzymes and contribute to insulin resistance, metformin can reduce insulin resistance by lowering free fatty acid levels. Metformin does not cause weight gain; it may actually reduce the body fat mass and produce weight loss in obese subjects. The UKPDS showed particular benefit of metformin therapy in obese diabetics over the use of sulfonylureas/insulin therapy in reducing both micro- and macrovascular endpoints.⁷

The half-life of metformin varies between 2 and 5 hours, with nearly 90% excreted via the kidneys. Due to its frequent gastrointestinal side effects such as diarrhoea, nausea and anorexia, it is recommended that metformin should be initiated at a low dose and titrated upwards gradually. The maximum daily dose is about 2.5 to 3 g in divided doses (Table IV). It is contraindicated in hepatic, renal, cardiac and respiratory failure, and should be used with great caution in any clinical setting associated with tissue hypoxia. Physicians using metformin should screen their patients for these contraindications, and monitor the renal function regularly, particularly in geriatric patients.

PPAR- γ Agonists and the 'Glitazones'

Peroxisome proliferator-activated receptor gamma (PPAR γ) is a nuclear hormone receptor acting as a ligand-dependent transcription factor that controls the expression of a large array of genes involved in adipocyte differentiation, lipid storage, cell proliferation, inflammatory processes, and modulation of insulin sensitivity.¹⁸ PPAR γ are located in adipose tissues, skeletal muscles and liver and are activated by a number of naturally occurring fatty acid derivatives. Synthetic compounds called thiazolidinediones (the "glitazones" for short) show high affinity for PPAR γ receptor and constitute a new class of oral therapeutic agent to reduce insulin resistance.

Like biguanides, thiazolidinediones do not affect insulin secretion. Its predominant antiglycaemic action is via increased expression of glucose transporters for peripheral glucose uptake. Glitazones also reduce hepatic glucose output by inhibiting gluconeogenesis.¹⁹ Troglitazone was the prototype PPAR γ agonist, but was discontinued from the market in March 2000 because of its potential in causing fatal hepatotoxicity. Rosiglitazone and pioglitazone are the currently available glitazones for therapy of type 2 diabetes, though only rosiglitazone is available locally.

The usual starting dose for rosiglitazone is 4 mg daily; the dosage can be doubled if indicated (Table IV). Because its action is mediated through gene transcription, the onset of action is slow and it may take up to 8 to 12 weeks before maximum benefit is attained. It is thus necessary to observe for improvement in glycaemic control over this period of time before titrating the dosage of the glitazone. Similarly, the insulin sensitising effect of glitazones persists for several weeks after discontinuation. On the average, the HbA1c can be expected to decrease by 1% to 1.5%.

The common adverse effects of glitazones include fluid retention and weight gain; the latter being contributed by factors such as fluid retention, fat deposition and overall improved metabolic control. Unlike troglitazone, hepatotoxicity is rare in rosiglitazone and pioglitazone. As

a precautionary measure, the glitazones are contraindicated in any patient who has baseline alanine aminotransferase (ALT) above 2.5 times the upper limit of normal. Liver enzyme measurement is recommended pre-treatment, and two monthly thereafter for a year. As glitazones are expensive drugs with a relatively high incidence of adverse effects, it is more prudent to use glitazones as add-on therapy to patients who fail conventional combination oral therapy.

Alpha-glucosidase Inhibitors – Acarbose

Alpha-glucosidase inhibitors such as acarbose, miglitol and voglibose delay the digestion and absorption of dietary polysaccharides by reversibly inhibiting the carbohydrate-digesting enzymes (glucoamylase, sucrase, maltase and isomaltase) and thereby attenuating postprandial hyperglycaemic excursions.

This class of drugs delays absorption of postprandial blood glucose via a non-systemic action, with digestion of carbohydrates most significantly retarded at the duodenum and jejunum. However, its glucose-lowering effect is modest with mean reduction in HbA1c of 0.5% to 1.0% only.²⁰ Acarbose can be initiated at a dose of 25 mg three times daily with meals, and the dose gradually titrated upwards if necessary to a maximum dose of 100 mg thrice daily in patients weighing over 60 kg (Table IV). In other countries, two more newer α -glucosidase inhibitors, miglitol and voglibose, are also available for the treatment of type 2 diabetes.

Alpha-glucosidase inhibitors are relatively costly and they are associated with a high prevalence of gastrointestinal side-effects like diarrhoea, abdominal discomfort and flatulence. Since α -glucosidase inhibitors target at the polysaccharide-digestive enzymes that reside only at the brush border of the gut, its antiglycaemic action is essentially non-systemic. Despite some degree of intestinal absorption, it is important to appreciate that α -glucosidase inhibitors exert no further glycaemia-blunting effect in the bloodstream due to the absence of polysaccharide-digestive enzymes in the systemic circulation. However, because these agents are absorbed systemically, they should not be administered during pregnancy and it is also not advisable to prescribe them to lactating women who breast-feed their babies. Generally, these drugs are relatively safe for patients with mild to moderate liver or renal impairment, though they should be avoided in severe renal failure as the plasma drug levels can be markedly elevated. As a practical point, patients on combination therapy that includes an α -glucosidase inhibitor who develop hypoglycaemia should be reversed with glucose and not sucrose (cane sugar), given that the breakdown of sucrose into glucose and fructose will be retarded by the α -glucosidase inhibitor.

eventually require two or more doses of insulin administration daily.

Multiple Insulin Injections

When glycaemic control remains poor despite BIDS regimen, it is reasonable to discontinue oral insulin secretagogues and switch to insulin therapy. However, insulin sensitizers can be used in conjunction with exogenous insulin administration to minimise the insulin dose. The most common insulin regimen consists of twice daily insulin administered before breakfast and dinner. For obese type 2 diabetics, the average daily dose of insulin approximates 1 U/kg body weight, while lean patients may be controlled with half the amount. Unless there is a definite pattern of hyperglycaemia and low blood glucose values, it is reasonable to split this dose equally between pre-breakfast and pre-dinner injections. In patients requiring more than 30 units of insulin daily, it might be preferable to use a mixture of short and intermediate acting insulins rather than intermediate or long-acting insulin only. This has been made convenient for the patients with availability of pre-mixed insulin preparations (e.g. Mixtard (30/70), Humulin (30/70) and Humalog Mix 25). Fine-tuning of insulin doses is best determined by home blood glucose monitoring profile and the glycaemic trend over time.

Insulin Analogues

Rapid-acting insulin analogues, such as lispro and aspart insulin, can be injected just prior to meals and thus obviate the need to wait 30 to 45 minutes before eating.^{28,29} Unlike regular human insulin, these analogues rapidly dissociate into monomers and dimers on subcutaneous injection, thus facilitating rapid absorption into the capillaries. Insulin lispro has a weaker tendency for self-association than human insulin because of the switch in the positions of lysine at position 28 and proline at position 29 of the β -chain. Insulin aspart is produced by substituting the proline at position 28 of the β -chain of insulin with negatively charged aspartic acid. Due to the rapid onset and shorter duration of action, these rapid-acting insulin analogues have a lower risk of hypoglycaemia than regular insulin.^{29,30} The potency of insulin lispro and insulin aspart is equivalent to regular insulin, except that it has much more rapid activity.

Long-acting insulin analogues, such as insulin glargine, which will be available soon in Singapore, mimics the insulin pump by providing basal insulin throughout the day due to its “peakless” pharmacokinetic profile. It is soluble and precipitates after injection, resulting in a long half-life with about 50% activity 24-hour post-injection.³⁰ Clinical trials of insulin glargine in both type 1 and type 2 diabetic patients confirmed its efficacy in improving fasting blood

glucose control and reducing the incidence of nocturnal hypoglycaemia.³⁰ While rapid-acting insulin analogues are generally not required for patients with type 2 diabetes mellitus, long-acting insulin analogues are expected to benefit patients with type 2 diabetes by providing a steady basal insulin delivery, thus reducing the risk of hypoglycaemia.

Summary and Practical Points

Although lifestyle modification with diet and exercise constitutes the cornerstone of type 2 diabetes management, pharmacologic interventions are inevitably required in the majority of patients. All the antidiabetic agents discussed can be used as monotherapy or in combination with one another. The choice of initial oral agent should be individualised and weighed upon various factors including the desired therapeutic targets, potential adverse effects, cost, compliance issues, etc.

Sulfonylureas and metformin continue to be the mainstay oral hypoglycaemic agents for type 2 diabetics because they are potent, cost-effective, and have established long-term efficacy and safety records. Metformin reduces hepatic glucose output and is particularly useful for obese type 2 diabetics. Alpha-glucosidase inhibitors, meglitinides and thiazolidinediones are newer classes of drugs with a unique place in the armamentarium for type 2 diabetes patients. Meglitinides are useful for patients with predominantly postprandial hyperglycaemia who are also at risk of hypoglycaemia with sulfonylurea therapy. Alpha-glucosidase inhibitors have a role in controlling post-meal hyperglycaemia, and may be used as monotherapy for those with mild diabetes. Thiazolidinediones constitutes a new class of insulin sensitisers and are particularly useful as add-on therapy in patients who failed to achieve satisfactory control with conventional combination therapy. If combination therapy with these available oral agents fail to attain glycaemic goals, adding on or switching over to insulin may be necessary. However, insulin therapy may be used upfront if the level of hyperglycaemia is clinically judged to be difficult to control using oral agents.

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QUESTIONS

1. Regarding the use of thiazolidinediones:
 - a) The onset of hypoglycaemic action is rapid
 - b) They have a gradual washout period
 - c) Contraindicated when ALT/AST >2.5x upper limit of normal
 - d) Are safe in patients with congestive heart failure
2. Hypoglycaemia is unlikely with monotherapy of the following agents:
 - a) Rosiglitazone
 - b) Acarbose
 - c) Metformin
 - d) Metiglinides
3. Compared with sulfonylureas, metiglinides:
 - a) Bind to a different receptor on the pancreatic β -cell
 - b) Are more potent insulin secretagogues
 - c) Are associated with a lower incidence of hypoglycaemia
 - d) Have a shorter serum half-life
4. The following antidiabetic agents are licensed for use in the pregnant diabetic:
 - a) Acarbose
 - b) Insulin
 - c) Metformin
 - d) Sulfonylureas
5. True statement(s) concerning α -glucosidase inhibitors include:
 - a) Non-systemic antiglycaemic action
 - b) No effect on the absorption of dextrose
 - c) Sucrose is effective in reversing hypoglycaemia in patients on acarbose
 - d) Contraindicated in advanced renal failure

ANSWER SHEET

Continuing Professional Development:
Current Therapeutic Strategies for Type 2 Diabetes Mellitus

Question 1

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 2

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 3

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 4

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 5

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

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