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Dr F Pirie, currently a member of the Diabetes and Endocrine Unit at the Nelson R Mandela School of Medicine, University of Natal, has interests in the pathophysiology of both type 1 and type 2 diabetes and the clinical management of subjects with type 2 diabetes in relation to preventive strategies.

Selection of oral agents in the management of type 2 diabetes

An understanding of how to manage type 2 diabetes depends on understanding the underlying causes of the disease.

PATHOGENESIS OF TYPE 2 DIABETES

The hyperglycaemia of type 2 diabetes develops when pancreatic β-cell insulin secretion is insufficient to compensate for the prevailing degree of insulin resistance. In the initial stages, postprandial hyperglycaemia occurs, but with progression, fasting hyperglycaemia also develops. In most people with type 2 diabetes, the disorder is a condition of both insulin resistance and β-cell dysfunction in different proportions. It appears that both components are required for the clinical expression of the disease.[1]

Rare conditions exist in which overt diabetes develops with either extreme insulin resistance alone or severe defects in insulin secretion alone, without the corresponding metabolic defect. Insulin resistance appears to be the initial metabolic defect in most subjects destined to develop the disease and is often demonstrable many years before the onset of any abnormality in glucose tolerance.[2,3] Evidence in favour of the presence of β-cell dysfunction was provided by the United Kingdom Prospective Diabetes Study (UKPDS), in which it was estimated that approximately 50% of β-cell function is lost by the time type 2 diabetes is diagnosed.[4] In addition, the UKPDS showed that β-cell function continued to decline over time, indicating that type 2 diabetes is a progressive disease.

Insulin resistance commonly occurs in association with obesity and the relationship between insulin sensitivity and body mass index (BMI) has been shown in numerous studies.[5] Not all obese subjects with insulin resistance develop diabetes, however, thus substantiating the fact that an additional factor (β-cell dysfunction) is required for the disease to develop. Furthermore, at least some of the β-cell dysfunction appears to be reversible by optimal glycaemic control.[6] In the early stages of the disease, improvement in insulin secretion through optimal glycaemic control may be sufficient to induce clinical remission for a variable length of time.

Not all obese subjects with insulin resistance develop diabetes, however, thus substantiating the fact that an additional factor (β-cell dysfunction) is required for the disease to develop.

The predominant metabolic disturbances which result from combined insulin resistance and inadequate insulin secretion include decreased glucose uptake by skeletal muscle and liver, decreased hepatic glycogen synthesis and increased hepatic glucose production. Insulin resistance at the level of the adipocyte causes increased lipolysis, resulting in an increase

in circulating free fatty acids with deleterious effects on both insulin sensitivity and insulin secretion (lipotoxicity).

Type 2 diabetes is classified as a single entity by the World Health Organisation, but is qualified as being due to either predominant insulin resistance or predominant insulin secretory dysfunction,[7] which means that the disorder is heterogeneous. Population-based prevalence studies have also shown ethnic heterogeneity.[8] Application of a common therapy to a condition with a uniform clinical expression (hyperglycaemia) but variability in the pathogenetic factors, is not logical. Clinical judgement is needed to select the most suitable therapies to treat hyperglycaemia in individual cases. Recognising that the disease is, in all probability, inexorably progressive despite optimal glycaemic control, is critical to the long-term follow-up of patients with type 2 diabetes. This requires continued surveillance of metabolic control and corresponding adjustment of therapy in all cases.

Recognising that the disease is, in all probability, inexorably progressive despite optimal glycaemic control, is critical to the long-term follow-up of patients with type 2 diabetes.

The UKPDS demonstrated that good glycaemic control can result in reduction of microvascular complications of diabetes.[4] This means that any clinician managing patients with type 2 diabetes must ensure that glycaemic targets are achieved and maintained as strictly as possible in each individual case. The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) has published guidelines for metabolic control and these include a fasting glucose concentration of 4 - 6 mmol/l, postprandial glucose concentration of 4 - 8 mmol/l and glycated haemoglobin level < 7.0%.[9]

Both non-pharmacological and pharmacological interventions can help attain these goals. Non-pharmacological interventions include weight loss through calorie-restricted diets and regular physical exercise. Both are effective in reducing hyperglycaemia and should be the initial management in most subjects with newly diagnosed type 2 diabetes.[10,11] Although diet and exercise will be insufficient as sole therapies for long-term management in most cases, they should remain part of the management, since drug therapy is more effective in subjects on continued diet and exercise programmes.[10,11]

Pharmacological therapy includes the oral agents and insulin. Insulin therapy is not discussed further, other than saying that it is probably a reality for most subjects with long-term type 2 diabetes, if glycaemic targets are to be maintained.

ORAL ANTIHYPERGLYCAEMIC AGENTS

A number of classes of agents have been approved for the management of type 2 diabetes mellitus and it is likely that the list will continue to expand as novel therapies are introduced. Each group of agents differ in terms of mechanism of action and advantages and disadvantages. Broad understanding of pathogenetic mechanisms of type 2 diabetes and the mechanism of action of individual drugs, allows tailoring of therapy in individual cases. The classes of agents in general clinical use are:

- sulphonylureas
- non-sulphonylurea insulin secretagogues
- biguanides
- α-glucosidase inhibitors
- thiazolidinediones.

Mechanisms of action and pharmacological properties of oral antihyperglycaemics

Sulphonylureas

Sulphonylureas bind to the SUR 1 subunit of the K_{ATP} channel, located on the β-cell surface membrane, resulting in the closure of ATP-sensitive potassium (K^+) channels. This inhibits K^+ efflux from the cell, resulting in depolarisation of the cell with subsequent opening of adjacent voltage-dependent L-type calcium (Ca^{2+}) channels. Intracellular Ca^{2+} levels increase, acting as the second messenger for insulin secretion and insulin is released in a biphasic manner, proportional to the intracellular Ca^{2+} concentration. Sulphonylureas augment endogenous insulin secretion and partially overcome the β-cell defect, but generally have a slow onset of action and relatively prolonged effect, resulting in both postprandial and fasting increase in insulin secretion. As a group, the sulphonylureas have a relatively weak effect on postprandial hyperglycaemia and a greater effect on fasting hyperglycaemia.[12]

There are a number of different sulphonylureas, broadly distinguished into first- and second-generation agents according to the date of release for clinical use (Table I).

Most of the sulphonylureas have inactive metabolites, the major exception being acetohexamide — the metabolites of this compound have 2.5 × the activity of the original molecule. Of the newer agents,

Table I. **Sulphonylureas**

	Duration of hypoglycaemic action (hours)
First generation	
Tolbutamide	6 - 10
Chlorpropamide	60
Acetohexamide	12 - 18
Second generation	
Glibenclamide	24
Gliclazide	Up to 24
Glipizide	Up to 24
Glimepiride	Up to 24

glibenclamide has a more sustained effect on the β-cell than the other agents and this translates into clinical experience of more frequent and severe hypoglycaemic reactions as compared with gliclazide, glipizide and glimepiride.

All sulphonylureas have a common sulphonylurea moiety, which confers the class effect, but each differs chemically in the side chains of the molecule. It is these chemical differences that confer different properties on each agent. For example, gliclazide has been reported to inhibit platelet adhesion and increase tissue plasminogen activator levels[13] and glimepiride has been reported to bind less avidly to the myocardial K_{ATP} channel than glibenclamide and thus reduce ischaemic pre-conditioning less than glibenclamide.[14] Whether these added effects have clinical relevance or not remains open for debate.

Non-sulphonylurea insulin secretagogues

There are two agents in this group — repaglinide and nateglinide.

Repaglinide

Repaglinide has a mechanism of action similar to the sulphonylureas except that it binds to the β-cell SUR 1 K_{ATP} subunit at a site distinct from that of the sulphonylureas. It induces insulin secretion in a similar manner. Repaglinide differs from sulphonylureas in the timing of both onset and offset of action. The T_{max} is in the region of 30 - 60 minutes and the $T_{1/2}$ (elimination half-life) is in a similar range. This results in a rapid burst of insulin secretion with a rapid offset of action. Clinically this results in better post-prandial glycaemic control than sulphonylureas and less between-meal hypoglycaemia. Repaglinide is metabolised in the liver and there are no active metabolites.

Nateglinide

Nateglinide is a phenylalanine derivative that binds to the same site on the β-cell SUR 1 subunit as glibenclamide,[15] but differs substantially from glibenclamide in its rapid association and dissociation from the receptor (in a manner analogous to that of repaglinide). Nateglinide has a more rapid onset of effect than repaglinide, but also a shorter duration of action.[12] Furthermore, nateglinide has no effect in the fasting state and appears to have a glucose concentration-dependent effect on the degree of insulin secretion.

Biguanides

Metformin is the only biguanide in clinical use worldwide. Despite many years of study, the primary mechanism of action of metformin is incompletely understood. Metformin decreases both gluconeogenesis and glycogenolysis and has a relatively small influence on enhancing peripheral insulin sensitivity.[12] Since there is no stimulation of insulin secretion, there is a negligible risk of hypoglycaemia with metformin monotherapy. Metformin is incompletely absorbed from the gastrointestinal tract, has a half-life of 1.5 - 3.0 hours and is excreted entirely by the kidney. During the absorptive process, endogenous lactate is produced and it is this property of the drug that is responsible for the major adverse effect, namely lactic acidosis.

Alpha-glucosidase inhibitors

These agents effectively induce a state of carbohydrate malabsorption. Complex carbohydrates, ingested with a meal, are degraded to oligosaccharides by amylase. Oligosaccharides are then degraded to monosaccharides by small-intestinal α-glucosidase enzymes. The binding of oligosaccharides to the α-glucosidase enzymes is competitively inhibited by the α-glucosidase inhibitors and the undigested carbohydrates pass into the lower small intestine and large intestine where digestion by bacterial fermentation occurs. These agents differ from other oral antihyperglycaemic agents in that they do not act systemically, they decrease both post-prandial glycaemia and post-prandial insulin secretion and they are not targeted at a specific pathophysiologic component of type 2 diabetes. The only member of this group available in South Africa is acarbose.

Thiazolidinediones

The most recent additions to the available oral antihyperglycaemic agents are the two currently approved thiazolidinediones, pioglitazone and rosiglitazone. The thiazolidinediones, as a group, are insulin sensitisers and act by binding to the peroxisome-proliferator-activated receptor gamma (PPARγ) family of nuclear receptors. The activated receptors bind to specific response elements on nuclear DNA and thereby regulate the

transcription of genes involved in carbohydrate and lipid metabolism.[12] The precise mechanism whereby the modulation of gene transcription translates into increasing insulin sensitivity is unknown. It has also been demonstrated that these agents increase the formation of adipocytes from pre-adipocyte stem cells, particularly in subcutaneous adipose tissue, and subcutaneous fat mass may increase by up to 8%. Thiazolidinediones are metabolised extensively in the liver and pharmacokinetics are not significantly affected by mild to moderate renal impairment.

Additional effects of thiazolidinediones include increase in high-density lipoprotein levels, reduction in triglyceride concentrations and a variable effect on low-density lipoprotein levels.[16] In addition, there is evidence of improved endothelial function and possibly an anti-atherosclerosis effect.

Clinical efficacy of monotherapy with oral antihyperglycaemic agents

Sulphonylureas

Most studies report a 1 - 2% mean reduction in HbA_{1c}, compared with placebo. In the UKPDS, treatment of 3 867 persons with sulphonylurea compared with diet over 10 years, resulted in 0.9% reduction of HbA_{1c}, whereas a study of 416 persons with glimepiride versus placebo over 14 weeks, resulted in 2.5% reduction in HbA_{1c}.[16]

There is progressive loss of β-cell function over time and it would be reasonable to assume that the capacity of the β-cell to respond to sulphonylureas would correspondingly diminish and possibly account for progressive loss of clinical efficacy — so-called 'secondary failure'. This phenomenon has implications for treatment of individual cases. There appears to be comparable efficacy of most currently used members of the sulphonylurea group. Studies that have compared glipizide versus glibenclamide and glimepiride versus glibenclamide have shown equivalent efficacy in terms of reduction of HbA_{1c}.[16]

Non-sulphonylurea insulin secretagogues

Repaglinide compared with placebo has shown reduction in HbA_{1c} of 1.7 - 1.9% and nateglinide compared with placebo has shown reduction in HbA_{1c} of 0.6 - 1.0%.[16] Repaglinide was more effective than troglitazone in a 22-week study of 256 subjects, but demonstrated equivalent efficacy with glibenclamide and metformin in separate studies.[16] By contrast, nateglinide was less effective than metformin in a study of 701 subjects over 24 weeks.[16] Thus, it appears that repaglinide is similar to sulphonylurea agents in terms of efficacy, but nateglinide is slightly less potent.

Biguanides

Metformin has been the subject of many studies, including recent trials, since it was re-introduced in the USA in 1995. Mean reduction in HbA_{1c} ranges from 0.8% to 3.0% (compared with diet or placebo).[16] In the UKPDS, there appeared to be specific advantages to therapy with metformin in that metformin showed a greater effect than chlorpropamide, glibenclamide or insulin for any diabetes-related endpoint all-cause mortality and stroke.[17] Metformin compared with gliclazide, glipizide, glibenclamide and chlorpropamide, has shown equivalent efficacy in terms of reduction in HbA_{1c}.[16]

Alpha-glucosidase inhibitors

Comparison of acarbose with placebo has shown reduction of HbA_{1c} ranging from 0.4% to 1.3% — somewhat smaller changes in glycaemia than have been observed with most of the other oral agents. Acarbose compared with metformin 850 mg bd and glibenclamide mean dose 4.3 mg daily showed equal efficacy, but the comparison with suboptimal doses (of metformin and glibenclamide respectively) is perhaps not valid.

Thiazolidinediones

Both pioglitazone and rosiglitazone are superior to placebo, with reductions in HbA_{1c} ranging from 1.1% to 1.5%.[16] A comparison of pioglitazone 45 mg daily, rosiglitazone 8 mg daily and troglitazone 600 mg daily in 3 consecutive series of patients showed similar reduction of HbA_{1c} after 2 - 4 months of therapy.[18] Comparison of troglitazone with metformin and glibenclamide has shown equivalent efficacy.[16]

Clinical efficacy of combination therapy with oral antihyperglycaemic agents

Given the presence of a number of different pathophysiological defects in subjects with type 2 diabetes and the ongoing reduction in β-cell secretory capacity, using different oral agents with different mechanisms of action is a rational approach to management. Studies that have compared adding a second agent with the addition of placebo, have shown that the reduction in HbA_{1c} by the addition of the second agent is approximately equal to that which would have been observed with monotherapy with that agent. The reduction is additive rather than synergistic.[16] For example, in the UKPDS, addition of metformin to sulphonylurea resulted in an additional reduction in HbA_{1c} of 0.6% compared with the sulphonylurea alone.

An unexpected and as yet unexplained finding in the UKPDS was the observation that addition of

metformin to sulphonylurea-treated patients was associated with a 96% increased risk of death compared with therapy with sulphonylurea alone.[17] This is thought to be a consequence of the small sample size of this particular analysis and has not been repeated in other studies. Other examples of monotherapy compared with combination therapy include:

- the addition of acarbose to metformin versus placebo, which resulted in 0.7% additional reduction in HbA_{1c}
- the addition of rosiglitazone to metformin, which resulted in an additional 1.2% reduction in HbA_{1c}, compared with the addition of placebo
- the addition of pioglitazone to metformin versus placebo, which resulted in 0.8% additional reduction in HbA_{1c}.[16]

Adverse effects of oral antihyperglycaemic agents

All oral agents used in the management of type 2 diabetes are contraindicated in pregnancy, in type 1 diabetes and in children.

Sulphonylureas

The major potential adverse effect of therapy with sulphonylurea agents is hypoglycaemia. Glibenclamide and chlorpropamide were both used in the UKPDS and both were associated with major hypoglycaemic events (0.4% for chlorpropamide and 0.6% for glibenclamide over 10 years), but these were less frequent than those recorded with insulin therapy (2.3% over 10 years).[4] As would be expected, the subjects treated intensively experienced more major hypoglycaemic events than those treated conventionally and there were more major hypoglycaemic episodes in the first years of the study than in the latter years of the study. This probably relates to the presence of a greater number of responsive β-cells earlier in the condition. The progressive loss of β-cell mass translates into less hypoglycaemia, but also less efficacy. There is also an association with weight gain and 2 - 5 kg increase in body mass is usual.[16]

Non-sulphonylurea insulin secretagogues

Both the agents in this group have the potential to induce hypoglycaemia, although less than that which occurs with sulphonylureas because of the rapid dissociation of the compounds from the β-cell and the resultant rapid 'on-off' effect on insulin secretion. Thus, particularly in the preprandial period, there is less glycaemic-insulinaemic mismatching as compared with sulphonylureas. Similarly, weight gain is less problematic. A disadvantage, rather than an adverse effect, is the need for three times daily (meal-related) dosing.

Biguanides

The two major adverse effects of metformin are gastrointestinal intolerance and lactic acidosis. Gastrointestinal intolerance may be reduced by dosing with meals and increasing doses slowly, but there remains a proportion of subjects who still cannot tolerate the abdominal cramps, bloating and diarrhoea that may accompany metformin therapy. Lactic acidosis can be avoided if the drug is not used in conditions where endogenous lactate production is inherently increased or where renal excretion of the compound is inhibited.

Contraindications to metformin therapy include:

- serum creatinine > 132 μmo/l in men and > 123 μmol/l in women
- congestive cardiac failure requiring medical therapy
- abnormal liver function
- severe obstructive lung disease with hypoxaemia
- age > 80 years
- in the perioperative period (temporary discontinuation)
- radiological procedures using intravenous contrast material (temporary discontinuation)
- any acute illness requiring hospitalisation, including dehydration (temporary discontinuation).[19]

An infrequent adverse effect of metformin is the development of vitamin B_{12} deficiency and haemoglobin and vitamin B_{12} levels should be checked periodically (annually) in subjects on long-term metformin therapy.

Alpha-glucosidase inhibitors

The inhibition of carbohydrate absorption, induced by therapy with these agents, leads to the frequent gastrointestinal adverse effects of α-glucosidase inhibitors — bloating, flatulence and diarrhoea. These effects are minimised by starting with smaller doses and increasing slowly, and they do improve with continued use. Apart from this, the agents are safe and free from systemic toxicity.

Thiazolidinediones

Troglitazone, the prototype thiazolidinedione, was introduced into clinical use in the USA in 1997

and withdrawn in March 2000 following several episodes of severe liver toxicity. Since the introduction of the two newer thiazolidinediones, pioglitazone and rosiglitazone, no reports of comparable hepatic toxicity have appeared. Despite this, there is still a recommendation to monitor liver function after initiating therapy with these agents.

Apart from concern over liver toxicity, the only clinically significant adverse effect noted has been fluid accumulation and a corresponding exacerbation of congestive heart failure. The reason for fluid retention is unknown, but appears to be worse in subjects on insulin therapy, in whom reduction in haematocrit by up to 15% may occur.[12] Weight gain is seen with thiazolidinedione therapy, partly due to fluid accumulation and partly due to the development of increased adipose tissue in subcutaneous (as opposed to visceral) sites. Hypoglycaemia does not occur with thiazolidinedione monotherapy.

Oral antihyperglycaemic agents available in South Africa

Table II shows the preparations licensed for use in subjects with type 2 diabetes (as monotherapy and in combination) that are available in South Africa.

TARGETING THERAPY AND RECOMMENDATIONS FOR CLINICAL USE

The newly diagnosed type 2 diabetic requires initiation of therapy with diet, exercise and lifestyle modification. Exercise programmes must take account of co-morbidities, especially ischaemic heart disease. Subjects who have marked hyperglycaemia at presentation (plasma glucose > 15 mmol/l) or who are severely symptomatic will require drug therapy from diagnosis, in addition to lifestyle and dietary measures.

Choice of initial therapy is based on the assumption that the more overweight the person is, as measured by BMI, the greater the degree of insulin resistance (Table III). Conversely, the assumption is that the leaner the subject, the greater the insulin sensitivity and the greater the β-cell dysfunction. This latter group of subjects, however, may harbour late-onset type 1 diabetes and must be closely observed as decompensation to overt type 1 diabetes may occur.

References available on request.

Table II. **Oral antihyperglycaemic agents available in South Africa**

Generic name	Trade name	Dose range	Manufacturer
Sulphonylureas			
Acetohexamide	Dimelor	250 mg daily - 1 500 mg daily	Quatromed
	Hypomide		Aspen
Chlorpropamide	Diabinese	250 mg daily - 500 mg daily	Pfizer
	Diabitex		Salters
Glibenclamide	Daonil	2.5 mg daily - 10 mg bd	Aventis
	Euglucon		Roche
	Glycomin		Aspen
	Norton-glibenclamide		Norton
	Rolab-glibenclamide		Rolab
Glipizide	Minidiab	2.5 mg daily - 30 mg daily	Pharmacia & Upjohn
Gliclazide	Diamicron	40 mg daily - 160 mg bd	Servier
	Glucomed		Parke-Med
	Glycron		Aspen
	Rolab-Gliclazide		Rolab
	Ziclin		Knoll
Glimepiride	Amaryl	1 mg daily - 8 mg daily	Aventis
Non-sulphonylurea secretagogues			
Repaglinide	Novonorm	0.5 mg tds - 4 mg tds	Novo Nordisk
Nateglinide	Starlix	120 mg tds - 180 mg tds	Novartis
Biguanides			
Metformin	Glucophage	500 mg daily - 1 g bd	Merck
	Rolab-Metformin		Rolab
Alpha-glucosidase inhibitors			
Acarbose	Glucobay	50 mg tds - 200 mg tds	Bayer
Thiazolidinediones			
Pioglitazone	Actos	15 mg daily - 45 mg daily	Eli-Lilly
Rosiglitazone	Avandia	2 mg daily - 8 mg daily	Smith-Kline-Beecham

Table III. **Recommended oral antihyperglycaemic therapy**

Initial therapy	3 - 4-month follow-up	6 - 12-month follow-up
BMI > 25 kg/m² • Normal renal and cardiac function: metformin • Abnormal renal function*: thiazolidinedione or • Cardiac failure†: sulphonylurea or non-sulphonylurea secretagogue **BMI ≤ 25 kg/m²** • Sulphonylurea	**Targets achieved** No change in therapy, continue with observation and regular review **Failure to achieve targets** • Adverse effects with metformin: change to thiazolidinedione monotherapy • Hypoglycaemia with sulphonylurea: change to non-sulphonylurea secretagogues • Maximal dose metformin: add sulphonylurea, non-sulphonylurea secretagogues or thiazolidinedione‡ • Maximal dose sulphonylurea: add metformin or thiazolidinedione‡ • Maximal dose thiazolidinedione: add metformin if overweight and sulphonylurea if lean	**Targets achieved** No change in therapy, continue with observation and regular review **Failure to achieve targets** • If still on monotherapy, add a second agent as above • If on 2 agents in maximal dose, insulin therapy is indicated

* If there is severe renal dysfunction (serum creatinine > 400 µmol/l), insulin therapy is indicated.
† Thiazolidinediones are contraindicated in class III or IV heart failure.
‡ In principle, the sequence of choice should be: sulphonylurea/metformin, followed by non-sulphonylurea secretagogues (if hypoglycaemia occurs with sulphonylurea), followed by thiazolidinedione (unless there is clinical suspicion of severe insulin resistance). This is in view of the cost of the thiazolidinediones.

IN A NUTSHELL

Type 2 diabetes is a heterogeneous condition characterised by varying degrees of both insulin resistance and insulin deficiency (due to pancreatic β-cell dysfunction).

Type 2 diabetes is a progressive disease, with continued deterioration in β-cell function occurring in the majority of affected persons.

Oral antihyperglycaemic therapy is adjunctive to diet, exercise and lifestyle management.

Five classes of oral antihyperglycaemic agents are available for clinical use in South Africa, each with specific advantages and disadvantages and broadly designated as 'secretagogues' and 'sensitisers'.

Attempting to match therapy (based on mechanism of action of the pharmacological agent) with perceived pathophysiology is a logical approach to a complex metabolic disorder, but continued surveillance of metabolic control and adjustment in doses are usual.

Combination therapy is needed in the majority of persons with type 2 diabetes.

Insulin therapy is a reality for most persons with type 2 diabetes, if metabolic targets are to be attained and maintained.