

## **Type 2 diabetes mellitus: an evolving therapeutic approach**

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### **SUMMARY**

**The ultimate or primary goal of therapy for type 2 diabetes is to prevent the mortality and morbidity related to the microvascular and macrovascular complications. It is increasingly obvious that to achieve this on a global perspective we will need to identify better and more effective strategies to prevent diabetes and its precursors, obesity and inactivity. Similarly, since a large percentage (at least 50%) of patients with type 2 diabetes are undiagnosed, we need to improve the implementation of strategies aimed at detecting this undiagnosed population. Without a diagnosis we will not prevent, detect or treat the complications of diabetes. Finally, therapy of type 2 diabetes is evolving as the evidence base for clinical decision-making grows and as new therapeutic options become available. The therapeutic approach has broadened considerably to include more intensive treatment of the diseases frequently associated with type 2 diabetes and major contributors to morbidity and mortality, namely hypertension and dyslipidaemia.**

### **Introduction**

The approach to the management of type 2 diabetes has changed in recent times (1,2). Change is likely to continue as the evidence base for clinical decision-making grows and as new therapeutic options become available. The therapeutic approach has also broadened considerably from a restricted concentration on glycaemic control, aimed at preventing microvascular complications, to an approach which while still including glycaemic control is now aimed more broadly to prevent both macrovascular and microvascular complications. This new approach has a growing evidence base.

The older approach emphasized (at least in theory) controlling plasma glucose levels using a combination of diet and exercise. The attitude to dietary goals has become more realistic. The initial weight loss target might be 3-4% of body weight, increased in individual patients who are successful in losing weight. Failure to gain weight over time should be viewed as a success. Increased physical activity, medical problems permitting, is now truly encouraged rather than the

previous 'lip service' approach. In both the old and newer approaches, if glycaemic control is inadequate pharmacological agents are added. The definition of inadequate control is now more clearly defined by glycosylated haemoglobin measurement. Target glycosylated haemoglobin concentrations are suggested (2). The natural history of pancreatic function in type 2 diabetes appears to be of progressive failure of insulin secretion; as a result more pharmacological therapy, eventually including insulin, is required with longer disease duration. Pharmacological therapy is therefore introduced and/or increased earlier than previously if glycaemic control targets are not met.

The traditional pharmacological agents are metformin, one of the sulphonylurea group or insulin. These agents can be used singly or in combination.

### **Metformin**

This is an old drug developed from French lilac. It has significant gastrointestinal side-effects that have limited its use, at least in part because it is not introduced with adequate

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precautions and patient information. In the United Kingdom Prospective Diabetes Study (UKPDS), metformin use in overweight patients with type 2 diabetes was associated with a 36% reduction in all-cause mortality (3). This arm of the UKPDS is not without its critics on methodological grounds (4); however, in the absence of better data, metformin should be the first-line pharmacological agent used in overweight patients (greater than 120% of ideal weight) with type 2 diabetes.

Metformin works predominantly by reducing hepatic glucose production. In Australia it is available as 500 and 850 mg tablets. The maximum dose is now regarded as 2500 mg per day rather than 3000 mg per day.

To use metformin effectively, it should be introduced at a low dose and increased slowly. It should be taken before meals but can be taken with meals to avoid side-effects if required. I instruct the patient to take 250 mg once daily before the evening meal for one week and then increase to 250 mg before breakfast and before the evening meal for the second week. If a higher dose is required to achieve the target glucose levels, the patient is instructed to increase the dose to 250 mg before breakfast, lunch and the evening meal for the next week. This stepwise increase can continue until appropriate glycaemic control is achieved or the maximum dose is reached. If gastrointestinal symptoms are experienced at any dose the patient should be encouraged to tolerate them if possible, as it can take up to 10 days for them to settle. If the symptoms fail to settle and a good glycaemic response has been achieved, the dose should be reduced to the previous maximum tolerated dose and additional therapy with other agents added as required. Metformin does not cause hypoglycaemia although hypoglycaemia occasionally occurs, as it may do in patients on no antidiabetic medication.

I use metformin in combination with insulin in patients who find that it helps them maintain dietary compliance.

The major serious side-effect of metformin is its propensity to promote lactic acidosis. This almost always occurs in the presence of a

contraindication, most frequently renal impairment. Metformin should not be used when there is significant renal impairment. There are rules about serum creatinine but one should also take into account the patient's age and attempt to calculate their glomerular filtration rate. I would recommend reducing the dose of metformin when the glomerular filtration rate falls below 50-60 ml per minute. Care should also be taken at times of tissue hypoxia and during episodes which might impair renal function, such as exposure to X-ray contrast medium.

### **Sulphonylureas**

There are many members of this class of agent. There are no convincing outcome data that would favour the choice of one agent over any other apart from their relative potencies. Variations in duration of action determine frequency of dosing. Sulphonylureas act by interacting with an islet membrane protein called the sulphonylurea receptor which closes an inward potassium channel and alters the rate of potassium efflux from the cell, resulting in depolarization and insulin release. This class may cause hypoglycaemia. They can be used as first-line therapy in patients with type 2 diabetes who are thin or as a second agent when diet, exercise and metformin alone are insufficient to control blood sugar levels. Most are excreted in the kidney, which makes treatment of patients with renal failure difficult. Glibenclamide has an active metabolite which accumulates in renal failure. Tolbutamide and glipizide are exceptions since they are metabolized predominantly in the liver.

Sulphonylureas have major drug interactions which can both increase or decrease their metabolism, decrease their clearance or cause displacement from albumin-binding sites thereby increasing the bioactive fraction. Chlorpropamide causes hyponatraemia and is no longer widely used in Australia.

### **Insulin**

Insulin is a useful safe drug with two significant drawbacks. It has to be given by subcutaneous injection and it can cause hypoglycaemia. These latter two characteristics have limited its use, sometimes

inappropriately. Patients with type 2 diabetes who are struggling to control their blood sugar levels on oral medication in combination with attempts at diet and exercise often benefit greatly from the introduction of insulin. Even if their blood sugar level control does not change many report feeling significantly better. If they are already adhering to some diet or exercise regimen often the glycaemic control improves significantly. It is the patients who are unable to comply with dietary requirements in type 2 diabetes who find that insulin merely stimulates their appetite and increases their food intake without achieving improved glycaemic control. Although we tend to remember this type of patient they are a minority.

Many insulin regimens have been used or trialed in patients with type 2 diabetes. The most suitable regimen will depend on the underlying pancreatic insulin reserve. Patients with no or very little insulin secretion are likely to require a more complicated insulin replacement regimen than patients who still have significant residual insulin secretion but not enough to control their hyperglycaemia. Many different approaches can be used. For example, some patients find it acceptable to take insulin in the evening to normalize their fasting sugar and continue with tablets through the day. The UKPDS demonstrated quite clearly that targeting a normal fasting sugar alone was inadequate in controlling blood sugar levels in the long term (5). Many if not all patients with the passage of time will need daytime insulin to control hyperglycaemia through the day. Daytime hyperglycaemia is an important contributor to average glycaemia as reflected by the glycosylated haemoglobin. Controlling daytime hyperglycaemia will lower the glycosylated haemoglobin and thereby lower the risk of diabetic complications. However, there is no evidence that postprandial glycaemia is of any particular or special importance (6).

I believe a strong case can be made for greater use of insulin in type 2 diabetes, particularly in the increasing number of younger patients whose glycaemic control is not perfect. With appropriate patient compliance it is often relatively easy to achieve near normal glycosylated haemoglobins.

**Newer agents**

**Possibilities**

To help visualize some of the potential options for new antidiabetic drug development consider Figures 1 and 2. Figure 1 demonstrates that in the fasting state blood

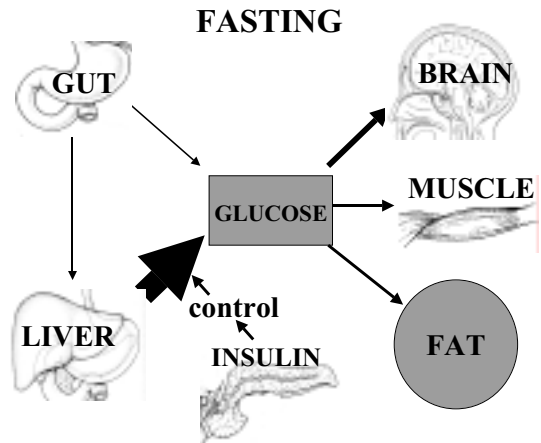


Figure 1. A simplified diagram showing the various contributions to plasma glucose concentration in the fasting state. The plasma glucose is maintained by glucose production from the liver (and to a lesser extent kidney). Glucose is utilized in non-insulin-sensitive tissues such as the brain.

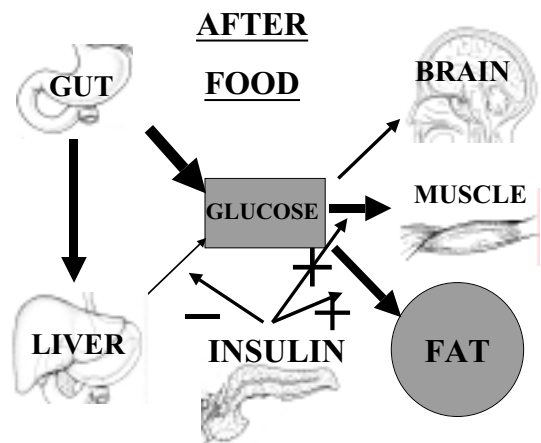


Figure 2. A simplified diagram of the various contributors to plasma glucose following a meal. Glucose is absorbed from the gut into the blood stream and also into the liver. Hepatic glucose production is reduced. Glucose is utilized in insulin-dependent tissues and increasingly in insulin-independent tissues such as muscle and fat. The decreased hepatic glucose production and the increased glucose utilization in insulin-sensitive tissues is regulated by insulin release from the pancreas.

glucose concentration is maintained by the controlled release of glucose from liver glycogen stores. During fasting with low but regulated insulin levels, glucose is used to supply non-insulin-sensitive tissues such as the brain. Fasting hyperglycaemia is due to the overproduction of glucose from the liver. The liver is the predominant site of action of metformin although it does have lesser effects of sensitizing muscle and fat to insulin. Figure 2 shows the more complex situation after food has been ingested. Nutrients including glucose, but not exclusively, are absorbed in the gastrointestinal tract. Glucose is taken up by the liver to replace glycogen stores and also contributes to the rising plasma glucose concentration. The rising glucose levels stimulate insulin secretion, which promotes glucose uptake into insulin-sensitive tissues such as muscle and fat. Postprandial hyperglycaemia in diabetes is due to a combination of effects which includes failure to appropriately suppress hepatic glucose production and failure to release enough insulin to stimulate uptake of glucose into muscle and fat. The inadequate insulin supply results from a beta cell insulin secretory capacity which is inadequate to overcome the tissue insulin resistance.

New drugs currently in use include those which reduce glucose or other nutrient absorption from the gut by a number of different mechanisms or those that increase insulin sensitivity in muscle, fat and the liver (Table 1). However, any component of the simplified system shown in Figures 1 and 2 is capable of being exploited to improve glycaemic control. In particular, drugs which would preserve beta-cell function to prevent its apparently inevitable decline or, even better, drugs which would replenish beta-cell numbers would obviously revolutionize the treatment of type 2 diabetes. Current laboratory work is targeting such classes of agents.

### **Insulin secretagogues**

Let us first look in Table 1 at the insulin secretagogues (agents which enhance insulin secretion). Traditionally sulphonylureas were the only class in this category. Now a new class of non-sulphonylurea insulin

**TABLE 1**

A LIST OF AVAILABLE AND POSSIBLE FUTURE ANTIDIABETIC DRUGS

#### **Insulin secretagogues**

Sulphonylureas

Non-sulphonylureas

– meglitinide analogues: repaglinide, others

Glucagon-like peptide (GLP-1)

#### **Insulin sensitizers**

Metformin

Thiazolidinediones

– Troglitazone (no longer used)

– Pioglitazone (15 to 45 mg per day given once daily)

– Rosiglitazone (2 to 8 mg per day given once or twice daily)

– Others

#### **Drugs that affect absorption**

Delaying gastric emptying

– GLP-1

– Pramlintide (an amylin analogue)

Inhibitors of  $\alpha$ -glucosidase

– Acarbose

– Miglitol

– Emigliatate

secretagogue has been released. This class works by a mechanism very similar to the sulphonylureas. They are non-sulphonylureas because they bind to a protein that is different from the classical sulphonylurea receptor but the effect is via the same potassium channels as are inhibited by the sulphonylurea receptor. From a practical point of view I would regard their actions as identical to that of the sulphonylureas. I have no personal experience in their use but it is possible that they may offer advantages in a limited number of cases when sulphonylureas cannot be used for reasons such as sulphur allergy or other side-effects.

In time it is likely that other insulin secretagogues will become available. Much work is being done on analogues of the glucagon-like peptide (GLP-1). This is part of the entero-pancreatic axis which sensitizes islets to respond properly to small rises in plasma glucose.

### **Insulin-sensitizing agents**

The most important new category of drugs are the insulin-sensitizing agents (Table 1). At present these are restricted to the thiazolidinediones also known as glitazones but non-thiazolidinedione insulin-sensitizing agents are being studied. The mechanism of the action of these drugs is not completely understood. They bind to and activate peroxisome proliferator-activated receptor-gamma (PPAR-gamma) receptors in fat cells and elsewhere, resulting in improved insulin sensitivity in fat, muscle and liver. Endogenous or exogenous insulin is required for their activity. They can be used as monotherapy, when they do not produce hypoglycaemia, or in combination with any of the other insulin therapies (7).

The first drug released in this class, troglitazone, produced an idiosyncratic liver reaction which resulted in fatalities. It was subsequently withdrawn from use. The next two agents likely to be marketed in Australia in the very near future are rosiglitazone and pioglitazone and others are likely to follow. These later agents appear not to produce the same idiosyncratic liver reaction although for safety reasons an increased frequency of liver monitoring is recommended. In Australia that will almost certainly be monitoring of liver function tests every second month. The other significant side-effects that will cause concern are weight gain and fluid retention. The weight gain is predominantly as peripheral fat (or fluid in some cases). There are data which suggest that intra-abdominal fat, the metabolically dangerous fat, is reduced. The fluid retention causes oedema in perhaps as many as 1 in 20 patients. It is currently recommended that these drugs are not used in the presence of New York Class Association heart failure 3 and 4.

### **Drugs affecting absorption**

The other new class of drugs, some of which are now available, are those that affect absorption of nutrients (Table 1). One subgroup simply delays gastric emptying. This results in a slower release of nutrients for absorption in the small intestine and that slows the rate of rise of plasma glucose. One such agent in clinical studies is derived from the amyloid protein commonly found in and around the islets of Langerhans in patients with type 2 diabetes. This protein was initially thought to produce insulin resistance but now is being trialed as a possible treatment through its ability to slow gastric emptying.

The second subgroup in this class consists of those drugs which inhibit gastrointestinal enzymes and prevent the absorption of free glucose or other nutrients. The inhibitors of glucosidases are one set of drugs in this subgroup which are marketed as antidiabetic agents. In Australia their role is limited to use in those people who have already failed conventional treatment with diet, exercise, metformin and/or sulphonylurea therapy and where an attempt is made to avoid insulin therapy. In my experience they are occasionally very effective in individual patients although on a group basis the improvement of glycaemic control which they achieve is rather modest. As might be expected they have a significant number of gastrointestinal side-effects which limit their use.

The other class of inhibitor which is available is orlistat (a gastrointestinal lipase inhibitor). In Australia this is marketed for its ability to promote weight loss and not for any role in lowering blood sugar level. The effect of these drugs on various metabolic parameters seems to parallel their ability to produce weight loss. Once again, as might be expected, they have a significant number of gastrointestinal side-effects which limits their use.

### **Cardiovascular disease**

Cardiovascular disease has a major impact on the mortality and morbidity of people with diabetes. This has been known for many years. Recent data from the National Health and

Nutrition Examination Surveys in the United States show that while heart disease mortality is falling in both men and women without diabetes, in women with diabetes there is an actual increase in mortality and in men with diabetes the decline in mortality is significantly less than in their nondiabetic counterparts .

The UKPDS demonstrated unequivocally that control of blood pressure to a mean of 144/82 mmHg significantly reduced both macrovascular and, interestingly, microvascular complications (8). Other studies support the importance of blood pressure control in patients with diabetes. Similarly, there is evidence that controlling dyslipidaemia in patients with diabetes also significantly reduces the risk of coronary heart disease (1). Although I am unaware of any direct study, it would seem reasonable to accept that smoking cessation would provide multiple benefits to patients with diabetes, not the least of which would be a reduction in their macrovascular risk.

This evidence has made it imperative that the management of patients with type 2 diabetes includes attention to the macrovascular risk factors, with particularly proactive aggressive management of hypertension and dyslipidaemia, in addition to control of glycaemia.

These recommendations are reinforced with specific goals or targets. The targets for blood pressure have been identified in two separate ways. Epidemiological studies demonstrate that in the general population the risks of end-organ damage appear to be lowest when the blood pressure is less than 120/80 mmHg. The UKPDS demonstrated benefits of treatment to at least 144/82 mmHg in type 2 diabetes (8). The older definition of hypertension as greater than or equal to 140 or 150/90 mmHg is no longer applicable. The target for blood pressure for patients with diabetes should at the very least be less than that achieved in the UKPDS and probably lower.

The primary goal of lipid therapy as recommended by the American Diabetes Association is for an LDL cholesterol of less than or equal to 2.6 mmol/l with targets for triglycerides of less than 2.3 mmol/l (1)

although some would argue that this should be 2 mmol/l.

In countries where resources are limited, targeted intervention of very high-risk subgroups of patients with type 2 diabetes may be appropriate to maximize resource utilization. This has been demonstrated to be successful in the Steno Study (9) where high-risk patients were identified and glycaemic control, blood pressure, dyslipidaemia and smoking were all targeted for aggressive therapy.

Separate aspects of the new approach to management of type 2 diabetes are:

- i) *Routine assessment for microvascular complications including regular foot examination, eye examination and assessment of nephropathy by the measurement of proteinuria usually as the albumin excretion rate.* The presence of subclinical abnormalities in any of these examinations should lead us to a reconsideration of therapies aimed at either directly preventing complications or generally minimizing complications. For example, patients with diabetes who are identified as having albuminuria are at significantly increased cardiovascular risk in addition to the risk of progression to diabetic nephropathy. These patients need even more aggressive treatment of their macrovascular risk factors together with specific therapies which might reduce the progression of their renal disease. Fortunately these therapies often overlap, such as control of blood pressure and lipids.
- ii) *Early detection of type 2 diabetes.* Many studies have shown that approximately half the population with type 2 diabetes are not diagnosed. Many have significant diabetic complications at the time of diagnosis. Diabetes needs to be diagnosed more promptly so that:
  - (a) advice and/or treatment to minimize the development of complications can be initiated

(b) treatment of existing complications can be initiated; ideally early diagnosis would identify complications at a subclinical stage.

(iii) *Disease prevention or, at the very least, delaying the onset of type 2 diabetes.* The prevalence of diabetes is increasing worldwide including in developing countries. This has been attributed to decreased activity and increased food intake. Intervention studies designed to increase physical activity or decrease food intake have demonstrated a reduction in the rate of progression to type 2 diabetes in high-risk populations (10).

Other studies have, incidental to their primary goal, shown that the selection of certain pharmacological agents used to treat the co-morbidities which are present in people at risk of developing diabetes, ie hypertension or dyslipidaemia, can reduce the rate of developing type 2 diabetes. The Hope study (11) demonstrated a significant reduction in the onset of new type 2 diabetes in patients treated with ramipril while in the West of Scotland Study there was a decreased incidence of diabetes in patients treated with Pravachol (12).

Prevention programs will require two different but interlocking approaches. Population strategies are required to increase activity and decrease caloric intake with a view to reducing the population burden of diabetes. A specific medical role will be to target high-risk individuals, for example women recognized as at risk of diabetes following a pregnancy complicated with gestational diabetes. In these high-risk groups, individual counselling can be undertaken and the choice of therapy to treat the co-morbidities should at least in part be influenced by the possibility that some of those therapies may reduce the likelihood of progression to type 2 diabetes. Smoking is now recognized as a risk factor for type 2 diabetes and smoking cessation should be recommended for this and a multitude of other reasons.

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