Type 2 diabetes

The pharmacotherapy of glycaemic control and risk factor modification

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BACKGROUND
Patients with diabetes have a high cardiovascular risk. In addition to achieving good glycaemic control, cardiovascular risk reduction is a vital component of management.

OBJECTIVE
This article summarises the pharmacotherapy of diabetes – both the achievement and maintenance of good glycaemic control, and the attenuation of co-existent cardiovascular risk factors.

DISCUSSION
Metformin is the first line hypoglycaemic agent when diet and exercise fail to achieve optimal glycaemia. The thiazolindinediones (glitazones) are effective new adjunctive oral hypoglycaemic agents that can be used in combination with either oral hypoglycaemics or insulin. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are beneficial in reducing long term complications of diabetes, especially in patients with microalbuminuria, hypertension, heart failure, previous acute myocardial infarction, and retinopathy. Statins are well established in both primary and secondary prevention in people with diabetes. Aspirin should be considered for primary prevention in patients with diabetes and increased cardiovascular risk.

Achieving optimal glycaemic control is the cornerstone of management in patients with type 2 diabetes for reduction in long term microvascular complications and prevention of diabetic emergencies. People with diabetes carry a 2–4 fold increased risk of cardiovascular mortality.[1] Hence, the cardiovascular risk factors need to be identified and treated aggressively. In addition to the critically important behavioural approaches of smoking cessation, increased physical activity and dietary modification, pharmacotherapy has a vital role to play in the management of type 2 diabetes.

Achieving optimal glycaemic control

Metformin

Case history
Mr SM, 54 years of age, attends your surgery for the first time. He was diagnosed 3 months earlier following a fasting blood sugar level (BSL) of 9.3 mmol/L and symptoms of hyperglycaemia. His body mass index (BMI) at presentation was 31 kg/m2 and his HbA1c 8.5%. He was commenced on a dietary and exercise program together with daily home glucose testing. At review he had not lost any weight and his fasting BSL averaged 9 mmol/L. His HbA1c was 8.1%. Mr SM was commenced on metformin 500 mg twice per day and given additional nutritional advice.

Metformin is generally considered the first line oral hypoglycaemic in type 2 diabetes provided there are no contraindications. It is an insulin sensitiser and predominantly acts by reducing the basal hepatic glucose production rate and by increasing peripheral utilisation of glucose. Most reports suggest that metformin treatment results in a 1.5–2.0% reduction in HbA1c and on average a reduction in fasting plasma glucose by 2.8–3.8 mmol/L.[2] Additional benefits include reduction in fasting triglyceride levels and LDL. It remains the only oral hypoglycaemic with strong evidence of reduction in macrovascular complications.[2] Usual initiation doses are 250–500 mg twice per day titrating upward to a maximum daily dose of 2–3 g. Metformin has also recently become available on the Pharmaceutical Benefits Scheme (PBS) in combination with a sulphonylurea (glibenclamide) in two strengths. It is also now available as a once per day slow release preparation.

Metformin is usually well tolerated and as it is not an insulin secretagogue, is not usually associated with hypoglycaemia. The most commonly reported side effect is gastrointestinal disturbance and diarrhoea, which is usually transient at initiation, and can be limited by using

a slower dose increment. A more serious but rare side effect is lactic acidosis, occurring at a rate of 0.3 per 100 000 patient years.[3] Patients most at risk are those with renal failure (eGFR <60 mL/min) or hepatic failure/chronic liver disease. The risk of lactic acidosis can be avoided by cessation of metformin in the setting of acute myocardial infarction or cardiac failure, severe sepsis, major surgery and following iodinated contrast administration. It is recommended that in the latter two situations, metformin be ceased 48 hours before the procedure.

Sulfonylureas

Sulfonylureas have traditionally been the most widely used oral hypoglycaemics in type 2 diabetes. They are insulin secretagogues, ie. they act by stimulating pancreatic insulin production. Five sulfonylureas that vary in their dosing, rapidity of action and half life are available on the PBS (*Table 1*).[4] Sulfonylureas can be used in combination with metformin when maximal tolerated doses have been ineffective in achieving glycaemic targets, or can be initiated as monotherapy where metformin is contraindicated. The average reduction in HbA1c and fasting glucose achieved with sulphonylureas is 1.1–2.0% and 3.3–3.9 mmol/L, respectively.[3,5,6] The choice of oral sulfonylurea depends on patient factors. Those drugs requiring once daily dosing may offer convenience for patients, or may be simpler for those taking multiple other medications. Longer acting sulfonylureas should be used with caution in those with renal impairment as they have a greater propensity to cause hypoglycaemia.

The major side effect is hypoglycaemia, as these agents increase the effective circulating insulin levels. There is no benefit in prescribing two sulfonylureas concomitantly.[3,5]

Thiazolindenediones (glitazones)

Case history

Mrs GF, 70 years of age, has an 8 year history of type 2 diabetes. Over the past 6 months her glycaemic control has deteriorated. She had maintained her fasting blood glucose measurements between 5.5–7.2 mmol/L on metformin 1000 mg twice per day and glimepiride 4 mg per day for the past 2 years. Her HbA1c was around 7.0%. However, despite no obvious change in her diet, the average fasting BSL has risen to 10 mmol/L and the most recent HbA1c was 8.3%. She has no symptoms of cardiac failure and has normal liver function tests (LFT). She is reluctant to commence insulin. Rosiglitazone 4 mg per day is commenced.

The glitazones are relatively new insulin sensitisers but have a different mode of action than metformin. Their action is mediated by binding with high affinity to the peroxisome proliferator activated receptor (PPAR–γ).[7] These compounds decrease insulin resistance and enhance the biological response to endogenously produced insulin, as well as insulin administered by injection. By reducing insulin resistance and improving insulin sensitivity, they result in a reduction of fasting plasma glucose, insulin, and free fatty acids.

When used as monotherapy they lower fasting plasma glucose by 2.3–2.9 mmol/L and the HbA1c by 0.5–1.5%.[6,7,9,10] It is important to warn patients that the onset of action of these agents is usually delayed with benefits not being seen for up to 6 weeks following initiation.

Pioglitazone is commenced at 15 mg increasing to a maximum daily dose of 45 mg, and rosiglitazone 4 mg with a maximal daily dose of 8 mg. Pioglitazone and rosiglitazone are available on authority on the PBS, but do have slightly different authority requirements. Pioglitazone is available as dual therapy with either metformin or a sulphonylurea in patients with HbA1c >7 in whom there is a contraindication to prescribing either metformin or a sulphonylurea or the patient is intolerant of either drug. Rosiglitazone is approved for use as triple therapy in combination with maximal tolerated doses of metformin and a sulfonylurea where optimal glycaemia has not been achieved (ie. HbA1c >7) or as dual therapy with either of those agents where combination therapy with metformin and a sulfonylurea is contraindicated or not tolerated. Neither drug is PBS listed as monotherapy.

When combined with insulin, the HbA1c is lowered by 0.6–1.2%.[6,9,10] Both pioglitazone and rosiglitazone are also PBS listed for use with insulin where insulin monotherapy, or insulin plus metformin, has failed to achieve adequate glycaemic control (ie. HbA1c >7%).[4]

The glitazones also exert a beneficial effect on the lipid profile with an 8–10% increase in HDL. Serum triglycerides tend to be reduced with pioglitazone, however there is little reduction in LDL.[9] Rosiglitazone however, tends to have less of a lipid lowering effect than its counterpart and may increase serum triglycerides and cholesterol.[7,10]

The major side effects of the glitazones are peripheral oedema and weight gain (1–4 kg over 6 months) in the form of increased subcutaneous but not visceral fat. Liver function tests should be performed before initiation of therapy and 2 monthly thereafter for the first year. These agents are contraindicated for use in patients with NYHA class III and IV cardiac failure, however, they can be used judiciously in those with milder degrees of cardiac failure.[7,9–10]

Alpha glucosidase inhibitors

Acarbose is the only available drug in this class. Its major effect is in delaying carbohydrate digestion and thus limiting postprandial hyperglycaemia. It has been demonstrated to lower the HbA1c by 0.5–1%.[11] The usual starting dose is 50 mg per day, titrating up to a maximal dose of 100 mg three times per day. Its main limiting side effect is gastrointestinal intolerance, mainly in the form of abdominal bloating, excessive flatulence and diarrhoea. Slow titration of acarbose can limit these effects. Hepatic transaminases may also be elevated and should be monitored in patients on acarbose.

Insulin therapy

At least 30% of patients with type 2 diabetes will eventually require insulin therapy. As type 2 diabetes is associated with insulin resistance, insulin requirements often exceed 1 unit/kg/day.[12,13] When initiating insulin therapy in patients with type 2 diabetes, insulin is often used in combination with the oral hypoglycaemic agents. Often an intermediate acting insulin (eg. NPH) is added at bed time. A typical starting dose would be around 0.1–0.2 units/kg.[13,14] The intermediate acting insulin is titrated to achieve fasting glycaemic targets (5–7.2 mmol/L) and an HbA1c <7.0%. If the patient has poor glycaemic control during the day, day time insulin can initiated; a twice per day regimen of insulin (isophane or premix intermediate/fast acting 30/70, 25/75, 50/50 or 20/80) or multiple daily injections. If the patient is taking an insulin secretagogue, this will generally be discontinued as insulin will now be replaced exogenously. However, the insulin sensitising oral agents (ie. metformin and glitazones) are often continued as insulin resistance remains the major underlying problem.[3]

Modification of diabetic complications and cardiovascular risk

While glycaemic control has proven to be of paramount importance in reduction of long term microvascular complications, it is critical that emphasis also be placed upon modification of other cardiovascular risk factors. The prevention of progression to renal disease, the treatment of dyslipidaemia, and the primary and secondary prevention of cardiovascular events, are equally as important as achieving optimal glycaemic control in patients with type 2 diabetes.[1]

The role of ACE inhibitors

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers (ARB) are not only a cornerstone in modifying cardiovascular risk and risk factors (hypertension) but are also used in preventing micro- and macro-vascular complications. Multiple trials have shown benefit of ACE inhibitors on subgroups of diabetes patients with microalbuminuria, renal disease, retinopathy and significant vascular risk.[15] However, despite their impressive risk lowering effects, there is no firm evidence to suggest that every patient with type 2 diabetes should be on either an ACE inhibitor or ARB in the absence of micro- or macro-vascular complications.

The United Kingdom Prospective Diabetes Study (UKPDS), the largest type 2 diabetes study, showed

Table 1. Available sulfonylureas[4]

Sulfonylurea	Trade name	Duration of action	Starting dose	Maximal dose
Gliclazide (80 mg)	Diamicron GenRx glicazide Glyade Nidem Mellihexal	12–18 hours	40 mg twice per day	320 mg/day
Gliclazide MR (30 mg)	Diamicron MR	20–24 hours	30 mg/day	120 mg/day
Glipizide (5 mg)	Minidiab Melizide	6–10 hours	2.5 mg/day/twice per day	20 mg/day
Glimepiride (1,2,3,4 mg)	Amaryl Diapride Dimirel	12–24 hours	1 mg/day	4 mg/day
Glibenclamide (5 mg)	Daonil Glimel	12–16 hours	2.5 mg/day/twice per day	20 mg/day
Metformin/glibenclamide (250/1.25, 500/2.5, 500/5 mg)	Glucovance	12–16 hours	500/2.5 mg/day/twice per day	2000/20 mg/day

Table 2. Criteria for prescription of statins[4]

Patient category	Lipid level for PBS subsidy
Patients with existing coronary artery disease	Cholesterol >4 mmol/L
Other patients at high risk with 1 or more of the following:	
• diabetes mellitus	Cholesterol >6.5 mmol/L, or
• familial hypercholesterolaemia	
• family history of coronary artery disease (first degree relative <60 years)	Cholesterol >5.5 mmol/L and HDL <1 mmol/L
• hypertension	
• peripheral vascular disease	
Patients with HDL <1 mmol/L	Cholesterol >6.5 mmol/L
Patients not eligible under the above	Cholesterol >7.5 mmol/L, or
• men 35–75 years of age	Triglyceride >4 mmol/L
• postmenopausal women up to 75 years of age	
Other patients not included in the above	Cholesterol >9 mmol/L, or Triglyceride >8 mmol/L

impressive benefits of achieving optimal blood pressure targets as well as blood glucose targets from the time of diagnosis.[5] Angiotensin converting enzyme inhibitors (Captopril) and ß–blockers (Atenolol) were found to be equally efficacious in reducing both micro- and macro-vascular complications. The available data suggest the better the blood glucose and blood pressure control, the less likely one is to develop diabetes related complications.

Proteinuria is a significant independent predictor of progression of renal failure, vascular disease, and cardiovascular and all cause mortality. Angiotensin converting enzyme inhibitors and ARB are antiproteinuric and protect against progression of renal failure. They are the first line agents used in patients with microalbuminuria, whether hypertensive or normotensive. Patients with diabetes and heart failure should also be on an ACE inhibitor unless contraindication or side effects prevent this.[15]

Statins

It is well established that patients with type 2 diabetes (and metabolic syndrome), even in the face of optimal glycaemic control, have an abnormal lipid profile. Dyslipidaemia is typically characterised by raised serum triglycerides, a small increase in the particularly atherogenic LDL and a decreased HDL.[16] High total cholesterol and diabetes both increase the cardiovascular risk, and together they more than double this risk.[16–17]

The Heart Protection Study[17] showed a 25% risk reduction in cardiovascular events with lowering of cholesterol in patients with type 2 diabetes. The evidence for statin therapy from this and other studies in patients with established coronary artery disease and diabetes is overwhelming. Additionally, this landmark trial demonstrated the benefit of statin therapy (simvastatin 40 mg) in primary prevention irrespective of the initial cholesterol. Another recently published study using atorvastatin demonstrated an approximately 35% reduction in cardiovascular events.[18] Despite this evidence, prescription of statin therapy is limited by PBS criteria (*Table 2*). (Statin therapy can be offered to diabetic patients who do not meet the PBS criteria on private prescription.) Statins are potent in lowering LDL and total cholesterol levels with a small reduction in triglycerides. The target LDL level in patients with type 2 diabetes is less than 2.5 mmol/L.

Recently, Ezetimibe has been demonstrated to reduce total cholesterol by approximately 20% either as monotherapy or in combination with a statin.[19] It is available on authority prescription where a statin is not tolerated or previous treatment with a statin caused significant toxicity. A new combination of ezetimibe 10 mg and both simvasatin 40 mg or 80 mg has recently become available on the PBS.

Which patients with diabetes should take aspirin?

Patients with type 2 diabetes have a 2–4 fold increase in the risk of mortality from cardiovascular disease.[1] Low dose aspirin (75–150 mg), used as a secondary prevention strategy for cardiovascular disease, has been well established for diabetes. It should be offered to all patients with diabetes following myocardial infarction, stroke, transient ischaemic attack, symptomatic peripheral

vascular disease and vascular bypass procedures, and stable ischaemic heart disease, provided there are no contraindications.[20]

Benefit of low dose aspirin as primary prevention of cardiovascular disease in patients with diabetes has been demonstrated in some studies. Patients most likely to benefit from its use include those over the age of 40 years with the additional risk factors of hypertension, smoking, dyslipidaemia, albuminuria and a family history of cardiovascular disease.[1,20] There is no evidence for clopidogrel use as primary prevention in patients with type 2 diabetes.

Summary of important points

- Metformin is the first line hypoglycaemic agent when diet and exercise fail to achieve optimal glycaemia.
- The thiazolindinediones (glitazones) are effective new adjunctive oral hypoglycaemic agents that can be used in combination with either oral hypoglycaemics or insulin.
- Patients with type 2 diabetes carry a 2–4 fold increased risk of cardiovascular mortality.
- ACE inhibitors and ARB are beneficial in reducing long term complications of diabetes especially in patients with microalbuminuria, hypertension, heart failure, previous AMI and retinopathy.
- Statins are well established in both primary and secondary prevention in people with diabetes and should be used in all patients with diabetes who meet the PBS criteria.
- Aspirin should be considered for primary prevention in patients with diabetes and increased cardiovascular risk.

Conflict of interest: none declared.

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