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Type 2 diabetes is a progressive disease and treatment of hyperglycaemia requires ongoing monitoring and modification. Many people will need to take oral antidiabetic agents and eventually most will require insulin. In this *NPS News* we touch on metformin, review the role of the thiazolidinediones (also known as 'glitazones') in type 2 diabetes and provide simple guidelines for starting insulin.

Metformin is the drug of first choice

Start metformin in people with type 2 diabetes who have inadequate glycaemic control (glycated haemoglobin HbA_{1c} > 7%) even after improving their diet and exercising for at least 30 minutes 5 times a week. The sulfonylureas (glibenclamide, glimepiride, gliclazide and glipizide) are an alternative if metformin is contraindicated or not tolerated.

In one of the largest clinical trials involving people with type 2 diabetes (UKPDS), metformin was significantly better than diet, insulin or a sulfonylurea at decreasing all-cause mortality, the incidence of diabetes-related complications and stroke among overweight people.¹

Use metformin with caution in the elderly, those with a heavy alcohol intake, among people with ischaemic heart disease and heart failure, and in people with impaired liver function. It should be avoided or discontinued in

people with impaired renal function (creatinine clearance < 30 mL/min) or a history of lactic acidosis.^{2,3} A reduced maximum dose of 1 g daily should be used in people with creatinine clearances of between 30 mL/min and 60 mL/min.²

Glycaemic control tends to deteriorate with time.^{1,4} When monotherapy fails, try combining metformin and a sulfonylurea to bring HbA_{1c} levels under control.

**This month's case study
(also available online at
<http://casestudy.nps.org.au>)
focuses on management
of persistent hyperglycaemia**



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Insulin or a glitazone?

Consider insulin when combining metformin and a sulfonylurea no longer provides adequate glycaemic control. Insulin reduces the risk of diabetes-related complications⁴ and has a well defined long-term safety profile.

Consider adding a glitazone (rosiglitazone or pioglitazone) for people who have a severe needle phobia or are very reluctant to use insulin, who require assistance from a third party to administer insulin, or whose employment may be threatened if they use insulin. Start insulin promptly if there is no response to the glitazone by 3 months.⁵

Adding insulin or a glitazone to metformin and a sulfonylurea results in similar improvements in blood glucose levels. In head-to-head trials among people whose glycaemia was inadequately controlled with metformin and a sulfonylurea, rosiglitazone, pioglitazone and insulin all reduced HbA_{1c} levels by around 1% to 2%.⁶⁻¹⁰ However, the long-term response and safety profile of glitazones compared with insulin is uncertain because all trials had 12 months or less follow up.

The glitazones may also be trialled with metformin or a sulfonylurea for those who cannot tolerate or have a contraindication to one of these drugs. The glitazone should replace the drug that is poorly tolerated or contraindicated. Insulin should be started promptly if the glitazone fails to control hyperglycaemia by 3 months.⁵

Glitazones effect on outcomes uncertain

As oral antidiabetic agents will be taken for many years, information on the effect of glitazones on clinical outcomes is vital. However, almost all the clinical trials of the glitazones used surrogate outcomes (e.g. changes in HbA_{1c}) instead of clinical outcomes (e.g. mortality, diabetes-related morbidity).

So far, only 2 trials have provided information on the impact of glitazones on clinical outcomes (Table 1).

PROactive investigated the effect of pioglitazone on cardiovascular morbidity and mortality in people with type 2 diabetes and a history of cardiovascular disease (excluding those with moderate or severe heart failure).¹¹ Pioglitazone added to existing therapies significantly improved a secondary outcome of all-cause mortality, myocardial infarction and stroke compared with placebo (hazard ratio 0.84, 95% confidence interval 0.72 to 0.98, p = 0.027).¹¹ But this should be treated with caution as this secondary outcome was not defined in the original protocol and the primary outcome was not significant.

RECORD is ongoing and aims to show that rosiglitazone combined with metformin or a sulfonylurea does not result in more deaths or hospitalisations due to cardiovascular events, compared with metformin and a sulfonylurea.¹² An unplanned interim analysis found no significant difference in the risk of cardiovascular death or hospitalisation after almost 4 years follow up.¹²

Table 1: Results of the primary, secondary and safety analyses of glitazone outcome trials

Source	Study population	Comparator	Primary outcome	Pros*	Cons*
PROactive Pioglitazone in addition to existing medications (N = 5 238)	Type 2 diabetes and cardiovascular disease	Placebo plus existing medications	Not significant 58 fewer primary events [†] with pioglitazone	57 fewer secondary events [‡] 42 fewer hospital admissions for diabetes 38 fewer cases of angina	115 more cases of heart failure 221 more cases of oedema 20 more cases of pneumonia Significant weight increase
RECORD Rosiglitazone and metformin or a sulfonylurea (N = 4 447)	Type 2 diabetes and no cardiovascular disease	Metformin and a sulfonylurea	Not significant 15 more primary events (cardiovascular death or hospitalisation) with rosiglitazone		21 more cases of heart failure

* Only significant differences shown.

† Secondary outcome was a composite of death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), or stroke.

‡ Primary outcome was a composite of death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg.

What are the risks of the glitazones?

Heart failure

People with type 2 diabetes are 2.5 times more likely to develop congestive heart failure than people without the disease.¹³ Glitazones also increase the risk of heart failure. In a large clinical trial, pioglitazone significantly increased the rate of heart failure compared with those receiving placebo (11% vs 8%, $p < 0.0001$).¹¹ Among people without any pre-existing cardiovascular disease, rosiglitazone doubled the risk of heart failure compared with the sulfonylurea glibenclamide (1.5% vs 0.6%, $p = 0.05$) and had a non-significant increased risk compared with metformin (1.5% vs 1.3%, $p = 0.52$).^{12,14}

Do not use glitazones in people with moderate or severe heart failure (New York Heart Association Class III or IV). In patients who are asymptomatic or have only mild cardiac insufficiency, glitazones may be used cautiously and should be started at the lowest dose.¹⁵ Prescribers and patients should be alert for symptoms of developing heart failure. Checking weight daily can provide an early warning of fluid accumulation.

Particular care should be taken when adding insulin to an existing treatment regimen that includes a glitazone. Patients should be started on a low dose and monitored closely for signs of oedema or rapid weight gain.

Myocardial infarction

Rosiglitazone may increase the risk of myocardial infarction.¹⁶ Do not prescribe rosiglitazone to people with known ischaemic heart disease, people using insulin or nitrates, and use with caution in people with a high risk for cardiovascular events.¹⁶

Pioglitazone does not appear to carry the same risk as rosiglitazone.¹⁷ However the meta-analysis from which this conclusion is drawn is limited as it relies heavily on the PROactive study (in which the primary outcome did not reach significance) and many of the other included trials were not designed to assess cardiovascular risk.

Weight gain

Weight gain is common to both rosiglitazone and pioglitazone with gains between 2 kg to 5 kg reported in the large clinical trials.^{11,14,18} Weight gain appears to continue for as long as people take glitazones: in 1 study, after 5 years of follow-up patients had gained 5 kg on average and their weight was still rising.¹⁴

Fractures

For every 100 women taking a glitazone for 1 year, there will be 1 additional fracture.^{14,19} In contrast to the vertebral fractures commonly seen among women with osteoporosis, these fractures are most likely to occur in the arms (humerus, forearm, hand, and wrist) or lower leg (foot, ankle, fibula and tibia).^{14,19}

Macular oedema

Macular oedema is a known complication of diabetes which may lead to worsening eyesight. There are reports suggesting an association between the glitazones and the development or worsening of diabetic macular oedema.²⁰

Potential liver toxicity

The first available glitazone, troglitazone, was withdrawn after it was found to cause unpredictable acute liver failure. While this risk appears to be significantly lower for rosiglitazone and pioglitazone, several cases of elevated liver enzyme levels, hepatocellular damage, hepatitis and, rarely, liver failure have been reported.^{21,22}

Do not prescribe glitazones to people with liver disease (including transaminase levels increased by more than 2.5 times the upper limit of normal). Perform liver function tests before starting a glitazone and 2 monthly thereafter, and monitor for signs and symptoms of liver toxicity (nausea/vomiting, jaundice, dark urine, right upper abdominal discomfort)²³ — with troglitazone, in some cases, normal enzyme concentrations progressed to irreversible liver failure within 1 month.²⁴

Don't delay using insulin

The progressive failure of the pancreatic beta-cells responsible for insulin production means that over time oral antidiabetic agents will no longer control hyperglycaemia.²⁵

People with inadequate glycaemic control despite making lifestyle changes and taking high doses of metformin and a sulfonylurea (and/or a glitazone) should start insulin without delay. Patients often see this as a major step and should be provided with encouragement and psychological support (Table 2).²⁶ Using the initiation of insulin as a threat to improve patient adherence to diet and lifestyle modifications or to medication use can worsen a patient's fear of insulin when the time to confront this choice eventually arises.

Table 2: Issues for discussion with patients about to start insulin^{26–28}

Fear	Advice
Insulin means I have failed	Type 2 diabetes is a progressive disease. It is the other treatment options that have failed, not the patient
Fear of injections	Insulin is injected into the fat layer under the skin, not into a vein. The fine, short needles available today do not hurt
Starting insulin is too difficult or complex	Insulin may be as simple as one injection at bedtime in addition to existing oral agents
Fear of hypoglycaemia	Severe hypoglycaemia is rare and occurs much less frequently in type 2 diabetes than in type 1 diabetes
I will gain weight	The long-term benefits of insulin outweigh the risks of modest weight gain. Explore ways of improving diet and increasing activity to counter any weight gain

Improving HbA_{1c} in people with type 2 diabetes requires reductions in average glycaemia. Blood glucose levels before main meals are the most important to target when the HbA_{1c} > 7.3%.²⁹ At this level of glycaemia, blood glucose is commonly elevated throughout the day, both before and after main meals. By improving the pre-meal blood glucose, postprandial values will also fall and this is why recent consensus algorithms for type 2 diabetes focus on basal rather than on bolus or rapid acting insulin.⁵

One of the simplest and safest ways to initiate insulin is to add night time basal isophane insulin to oral antidiabetic agents.²⁷ A simple approach to starting insulin is set out below (Table 3).

Table 3: Stepwise guide for initiating and adjusting insulin^{4,26,27,30}

Step 1	ADD 10 Units isophane insulin at bedtime. CONTINUE metformin, a sulfonylurea or both (at the same dosage, but no greater than the maximum recommended dose) <ul style="list-style-type: none"> • If evening blood glucose level is high then use 10 units morning isophane insulin. • If both morning and pre evening meal blood glucose levels are high then consider using twice-daily isophane. 												
Step 2	ADJUST insulin therapy gradually every 3–4 days according to fasting blood glucose (FBG) level until target FBG is reached (usually 4.0–6.0 mmol/L)* <table border="1"> <thead> <tr> <th>Mean FBG (mmol/L)</th> <th>Insulin dose</th> </tr> </thead> <tbody> <tr> <td>> 10</td> <td>Increase by 8 units</td> </tr> <tr> <td>8–10</td> <td>Increase by 6 units</td> </tr> <tr> <td>6–8</td> <td>Increase by 2 units</td> </tr> <tr> <td>4–6</td> <td>No change</td> </tr> <tr> <td>< 4</td> <td>Decrease by 2–4 units</td> </tr> </tbody> </table>	Mean FBG (mmol/L)	Insulin dose	> 10	Increase by 8 units	8–10	Increase by 6 units	6–8	Increase by 2 units	4–6	No change	< 4	Decrease by 2–4 units
Mean FBG (mmol/L)	Insulin dose												
> 10	Increase by 8 units												
8–10	Increase by 6 units												
6–8	Increase by 2 units												
4–6	No change												
< 4	Decrease by 2–4 units												
Step 3	CHECK overall blood glucose control with HbA _{1c}												
Step 4	If FBG and evening blood glucose are on target but HbA _{1c} is not, look for hidden 'hypers' — blood glucose peaks that occur during the day, often before lunch or after dinner <p>Options to correct hidden 'hypers' include:</p> <ul style="list-style-type: none"> • changing preceding meal size or composition • increasing activity after meals • adding acarbose • adding a meal time rapid acting insulin[†] 												

* A GP, trained practice nurse, credentialled diabetes educator or the educated patient can adjust insulin dose according to this titration schedule. Adjusting the insulin dose gradually can gain patient confidence and reduce the risk of hypoglycaemia.^{4,31}

† Biphasic or pre-mixed insulin are convenient but require a more strict adherence to the size and timing of meals and dosing can be inflexible leading to blood glucose fluctuation.²⁷

Don't delay using insulin (cont'd)

Continue oral therapy

Patients should not be automatically taken off their oral antidiabetic agents when they start insulin. Doing so can lead to a rapid rise in HbA_{1c} as the blood glucose lowering effects of the oral agents wear off. Continuing oral agents often means that patients only require a single, daily injection and allows insulin dosage to be titrated gradually until acceptable HbA_{1c} levels are achieved.^{27,32}

Combining metformin and/or a sulfonylurea with a single, daily injection of isophane insulin results in similar levels of glycaemic control to insulin monotherapy, with less weight gain and lower insulin doses.³³

Continue using metformin when initiating insulin — sulfonylureas are often also maintained but can be discontinued if hypoglycaemia develops.³²

If a patient is taking a glitazone, consider stopping it once they begin using insulin. Continuing the glitazones after initiating insulin treatment increases the risk of fluid retention, heart failure and weight gain.¹⁵ Combining rosiglitazone and insulin may increase the risk of an ischaemic event.³⁴

Evidence supports isophane as initial basal insulin therapy

A basal night-time isophane insulin while continuing oral antidiabetic agents is one of the simplest and safest ways to initiate insulin.²⁷

Basal insulins aim to provide a constant level of insulin between meals without producing hypoglycaemia. Isophane lasts 16 to 24 hours with a peak between 4 and 6 hours after injection. Insulin detemir (Levemir) lasts 12 to 20 hours with a peak at 9 hours. Insulin glargine (Lantus) last for 24 hours and has no peak.²

Isophane, glargine and detemir similarly improve HbA_{1c} levels among people with type 2 diabetes.^{35,36} The risk of severe hypoglycaemia is similar for all three basal insulins.^{35,36} The risk of nocturnal hypoglycaemia is lower with glargine and detemir than with isophane.^{35,36} However, there is a lack of information on the long-term safety of glargine and detemir and as such the use of these newer long-acting insulin analogues should be approached

cautiously.^{35,37} Reserve glargine and detemir for people who have symptomatic or nocturnal hypoglycaemia when using isophane.³⁷

Further information about insulin glargine can be found in the December 2006 *NPS RADAR* (www.npsradar.org.au).

Fixed-dose combination insulins (also known as biphasic or pre-mixed insulins) containing isophane and a rapid acting bolus insulin analogue (NovoMix 30, Humalog Mix 25 or Humalog Mix 50) given daily just before the main evening meal are an alternative to basal night-time isophane insulin, particularly in people where the evening meal is their largest. However, this approach increases the risk of post-prandial hypoglycaemia and titration can be difficult as the fixed combination nature of biphasic insulins means that increasing the basal dose also increases the dose of the rapid acting analogue which further increases the risk of post-prandial hypoglycaemia.²⁷

Adjusting insulin doses

Once insulin is commenced, gradual dosage adjustment should be informed by monitoring of blood glucose levels, any hypoglycaemia, and subsequent HbA_{1c} levels. Increase the dose every 3 to 4 days as per Table 3 until the target fasting blood glucose is reached.²⁷

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.



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