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Type 2 diabetes

Controlling hyperglycaemia with early insulin use

Background
Many patients with type 2 diabetes need to progress to insulin use when oral glucose lowering therapies fail to maintain adequate glycaemic control.

Objective
To suggest when and how to initiate insulin therapy for patients with type 2 diabetes in the primary care setting.

Discussion
In general, initiation of insulin should be considered in individuals on maximal tolerated doses of metformin and sulfonylureas with HbA1c levels >7.0% over a 3–6 month period. Current Australian guidelines recommend initiating insulin therapy as once daily basal therapy or as premixed insulins.

Keywords: blood glucose; haemoglobin A, glycosolated; general practice; diabetes mellitus, type 2; insulin therapy

Type 2 diabetes is characterised by insulin resistance, a progressive decline in beta-cell function, and worsening hyperglycaemia. HbA1c levels of <7.0% remain the target for good glucose control but individualisation of glycaemic targets has been advocated by the Australian Diabetes Society (*Table 1*).[1]

Many patients with type 2 diabetes need to progress to insulin therapy when oral glucose lowering therapies fail to maintain good glycaemic control. However, when and how to start insulin in type 2 diabetes are questions that are often without unequivocal answers.

The initiation of insulin therapy should be considered in individuals on maximal tolerated doses of metformin and sulfonylureas who have suboptimal glycaemic control (HbA1c >7.0%) over a 3–6 month period. Patients on maximal oral glucose therapies who present to their general practitioner with symptomatic hyperglycaemia, clearly have suboptimal control (HbA1c >9.0% and blood glucose levels >15 mmol/L) should start on insulin therapy as soon as possible.

NHMRC guidelines

The Australian National Health and Medical Research Council (NHMRC) guideline for blood glucose control in type 2 diabetes has recently been released.[2] This guideline suggests a stepwise approach to managing glucose levels starting with lifestyle modification, the initial use of metformin followed by the addition of a sulfonylurea, and then possible progression to insulin therapy (*Figure 1*), and recommends initiating insulin as once daily basal therapy or as premixed insulins.

The Australian Pharmaceutical Benefits Scheme (PBS) also subsidises the addition of sitagliptin or a glitazone to metformin therapy if a sulfonylurea is contraindicated or not tolerated. The converse also applies to patients who are taking sulfonylureas in whom metformin is contraindicated or not tolerated.

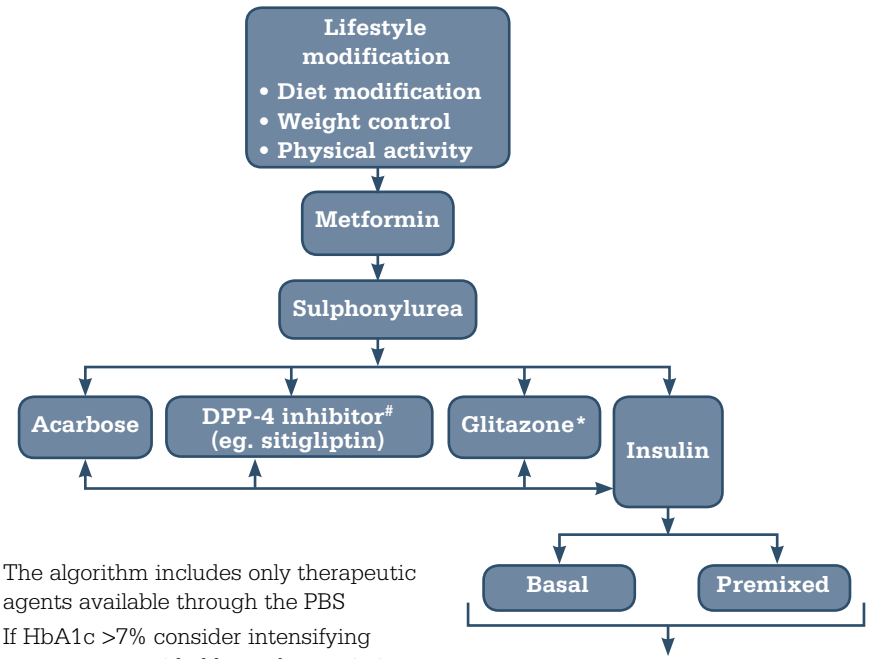
The NHMRC guideline recognises that progression to triple oral therapy can occur under certain circumstances. Under PBS guidelines this would involve a combination of metformin, sulfonylurea and pioglitazone or acarbose. Another possible option of triple therapy is metformin, sulfonylurea and the dipeptidyl peptidase (DPP-4) inhibitor sitagliptin, but this combination is not currently supported by the PBS.

The use of a glucagon-like peptide 1 (GLP_1) agonist such as exenatide also appears to be a useful glucose lowering therapy that promotes weight loss and does not cause hypoglycaemia when used in combination with metformin. Barriers to its use include its side effects profile, mainly nausea and vomiting, and lack of PBS subsidy. It should be noted that cardiovascular and mortality outcomes for agents that target the incretin system (such as sitagliptin and exenatide) have yet to be

Table 1. Summary of suggested HbA1c targets as advocated by the Australian Diabetes Society[1]

Duration of disease	CVD	Treatment	HbA1c (%)
Short	No	Diet/metformin	≤6.0
Short	No	SU	≤6.5
Short	No	Insulin	≤7.0
Long duration of disease or CVD			≤7.0
Problems with hypoglycaemia			≤8.0
The general HbA1c target remains			≤7.0

SU = sulfonylureas; CVD = cardiovascular disease



- The algorithm includes only therapeutic agents available through the PBS
- If HbA1c >7% consider intensifying treatment, provided hypoglycaemia is not a problem

PBS authority only as dual therapy with metformin or sulphonylurea where combination metformin and sulphonylurea is contraindicated or not tolerated

* Rosiglitazone is not PBS authorised for triple therapy or for use with insulin (from February 2009) but is approved only as dual therapy with metformin or sulphonylurea where combination metformin and sulphonylurea is contraindicated or not tolerated

Figure 1. Management algorithm for blood glucose control in type 2 diabetes[2]

documented in large, long term clinical studies. An international trial to test the cardiovascular safety of sitagliptin has recently commenced.

In general, the authors would recommend that insulin therapy be initiated, instead of progression to triple oral therapy, for patients on maximal tolerated doses of metformin and sulfonylurea if symptoms of hyperglycaemia are present and/or if HbA1c levels are >8.5%. If triple oral therapy is used, patients need to be closely monitored for the development of side effects (ie. weight gain and fluid retention with pioglitazone) and their glycaemic response. If a significant glycaemic response is not observed (a drop in HbA1c of approximately 1.0%) after 3–4 months of treatment, then insulin should be commenced and the third oral agent withdrawn quickly. If twice daily premixed insulin is used, then the sulfonylurea should also be withdrawn, but in a more gradual fashion.

Insulin regimens

The various options for initiating insulin therapy in type 2 diabetes are summarised in *Table 2*. The simplest regimen for initiating insulin is to start a bedtime dose of basal insulin (*Figure 2*). Basal insulin analogues, such as glargine and detemir (not currently supported by the PBS), with longer, nonpeaking profiles decrease the risk of hypoglycaemia compared with isophane (Protaphane and Humulin NPH) but no studies have clearly demonstrated that initiating insulin therapy with basal analogues, as opposed to isophane, improves HbA1c levels. Currently available basal insulins are shown in *Table 3* and their action profiles are shown in *Figure 3*. Most guidelines suggest starting basal insulin at around 10 units at bedtime. However, a morning dose alone or in combination with a bedtime dose of basal insulin could be considered in patients with elevated daytime blood glucose levels.

Another approach to starting insulin therapy is the initiation of twice daily premixed insulin (*Figure 4*). The rapid/short acting insulin in the mixture targets postprandial hyperglycaemia and can be used if daytime hyperglycaemia predominates. Generally a dose of 10–20 units is commenced at around breakfast time and a dose of 8–12 units is commenced at around dinnertime.

Mixed insulins containing rapid acting analogues can be injected at mealtimes, whereas preparations containing short acting, neutral insulin should be injected 30 minutes before meals to allow for their relatively slower onset of action. A summary of available premixed insulins is shown in *Table 4*, and the action profiles of premixed insulins are shown in *Figure 5*.

Initiating basal insulin should especially be considered in patients with HbA1c levels <8.5%, whereas for patients with higher HbA1c levels we recommend starting premixed insulin, especially if daytime hyperglycaemia predominates.

Insulin and oral glucose lowering agents

Most guidelines recommend initially maintaining both metformin and sulfonylureas (if tolerated or not contraindicated) after insulin therapy is initiated. This approach is generally associated with less weight gain and better glycaemic control. For patients initiated on basal insulin at bedtime, these oral agents should continue in an attempt to control

Table 2. Options for initiating insulin treatment in type 2 diabetes
Bedtime use of basal insulin
Isophane (Protaphane or NPH)
Glargine/Detemir*
Once or twice daily premixed (rapid/short and basal) insulin
Mixed (neutral/isophane) insulin (ie. Mixtard 30/70 and 50/50 or Humulin 30/70)
Mixed (rapid analogues/protamine) (ie. Humalog Mix 25 and Mix 50 or Novomix 30)
* Not subsidised by the PBS for type 2 diabetes

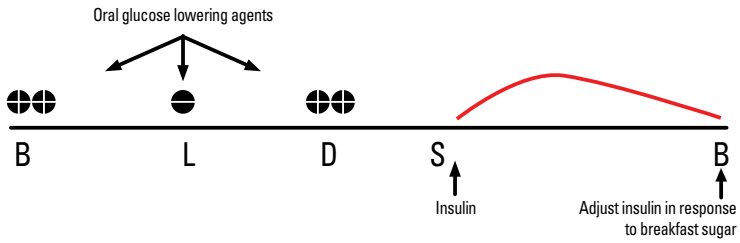


Figure 2. Initiating insulin therapy in type 2 diabetes – bedtime basal therapy

daytime hyperglycaemia. For patients commenced on premixed insulin, metformin and sulphonylureas should also initially continue. However, as glycaemic control improves, sulfonylureas can be weaned off and metformin continued. The combination of metformin and insulin has been shown to improve body weight, glycaemic control, insulin requirements and the risk of macrovascular disease in comparison to the use of insulin alone.[3]

How to titrate and intensify insulin therapy

Once insulin therapy is started, a plan needs to be in place for the appropriate adjustment of insulin doses. The key to adjusting insulin doses is 'pattern recognition'. A simple schedule for retrospectively modifying doses of insulin after it is initiated as either a bedtime basal therapy or a twice daily premix preparation is presented in *Figure 6* . When fasting, glucose levels are not at target, this generally means an adjustment to the dinnertime or bedtime dose of insulin (*Figure 2, 4* and *6*). When daytime or predinner glucose levels are not at target, this generally means an adjustment to the morning dose of insulin is required (*Figure 4* and *5*). Usually insulin doses are adjusted in 2–4 unit increments in response to the average glucose level at one particular timepoint over a period of approximately 3–4 days until patients can achieve an average BSL <7 mmol/L. If this general target can be achieved without causing hypoglycaemia then patients may be encouraged to aim for stringent targets, ie. achieving fasting blood glucose levels of 4–6 mmol/L on a long term basis (the target range advocated by The Royal Australian College of General Practitioners).[4]

Schedules for adjusting doses of insulin after its initiation in type 2 diabetes, according to target glucose levels, have been validated in large clinical studies and are available to guide dose adjustments for basal therapy (Treat-to-Target Trial)[5] or premixed preparations (INITIATE study).[6] However, the usefulness of these schedules outside of the clinical trial setting has not been evaluated. It should be stressed that patients should not necessarily react to a 'one off' glucose reading that is out of range, but should wait for a pattern to develop over a period of a few days before adjusting their insulin doses. An overall approach of retrospective adjustment of insulin doses instead of a reactive 'sliding scale' approach should be emphasised.

Patients should also be encouraged to make temporary adjustments to their insulin doses such as increasing or decreasing the dose of insulin by 2–4 units at mealtimes if more or less carbohydrate than normal is to be eaten, and decreasing their insulin dose by 25–50% if increased physical activity is planned. Future adjustments should then be modified according to the patient's subsequent glycaemic response to initial dose titrations. Although patients should be encouraged to adjust

Table 3. Basal human insulins				
Insulin	**Delivery devices**	**Onset**	**Peak**	**Duration of action**
Isophane (Protaphane)	3 mL penfill 10 mL vial 3 mL novolet 3 mL innolet	2–4 hours	4–8 hours	8–12 hours
Isophane (Humulin NPH)	3 ml penfill 10 mL vial	2–4 hours	4–8 hours	8–12 hours
Glargine (Lantus)	3 mL penfill 3 mL SoloStar pen	2–4 hours	No peak	20–24 hours
Detemir (Levemir)	3 mL penfill 3 mL flexpen	2–4 hours	No peak	12–18 hours

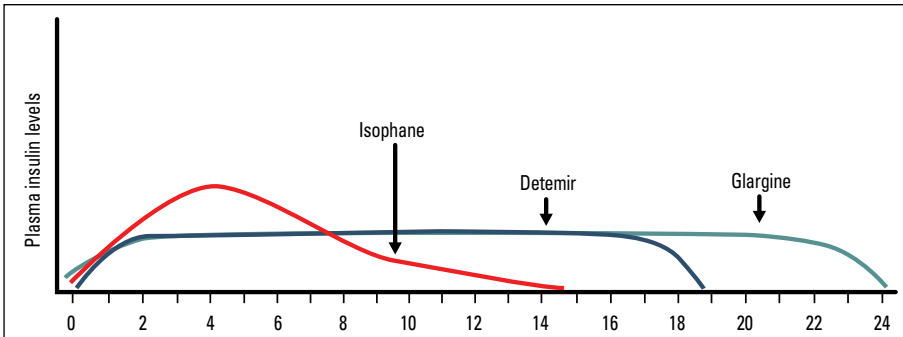


Figure 3. Basal insulin action profile

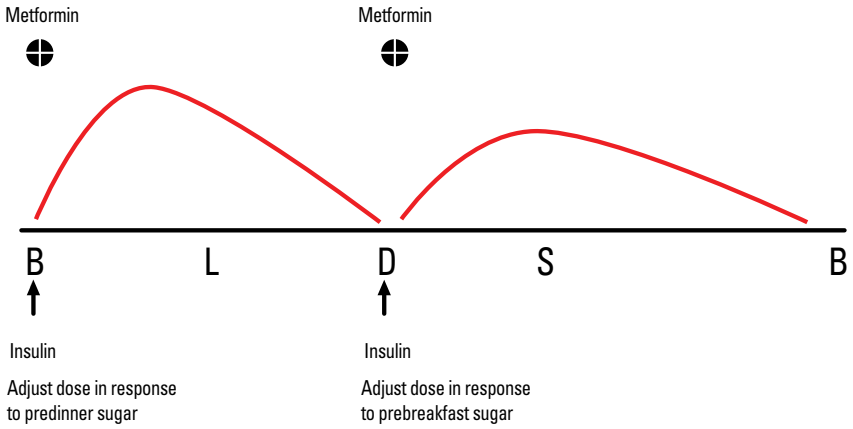


Figure 4. Initiating insulin therapy in type 2 diabetes – twice daily premixed therapy

Table 4. Premixed insulins

Insulin	Delivery devices	Onset	Peak	Duration of action
30% neutral/70% isophane				
Mixtard 30/70 Humulin 30/70	3 mL penfill 3 mL innolet 3 mL penfill 10 mL vial	30–60 minutes	Dual	8–12 hours
50% neutral/50% isophane				
Mixtard 50/50	3 mL penfill	30–60 minutes	Dual	8–12 hours
30% aspart/70% protamine				
Novomix 30	3 mL penfill 10 mL vial 3 mL flexpen	5–15 minutes	Dual	8–12 hours
25% lispro/75% protamine				
Humalog mix 25	3 mL penfill 3 mL kwikpen	5–15 minutes	Dual	8–12 hours
50% lispro/50% protamine				
Humalog mix 50	3 mL penfill 3 mL kwikpen	5–15 minutes	Dual	8–12 hours

their own insulin doses, regular clinical reviews and contact with a diabetes educator and GP are invaluable in assisting patients to optimally adjust their insulin doses.

If HbA1c targets are not reached with basal insulin, there are several options available for intensifying insulin therapy. One option for patients on once daily basal insulin is to change to twice daily premixed insulin preparations. However, introducing a second dose of basal insulin or a dose of rapid/short acting insulin with the largest meal of the day are other options. The natural progression from adding one rapid/short acting insulin injection would then be to a basal/bolus (three injections with meals) approach. For patients on twice daily premix insulin, one approach is to offer an injection of rapid/short acting insulin at lunchtime if predinner hyperglycaemia predominates. However, it is possible that a similar effect can be achieved with a third injection of premixed insulin at lunchtime.

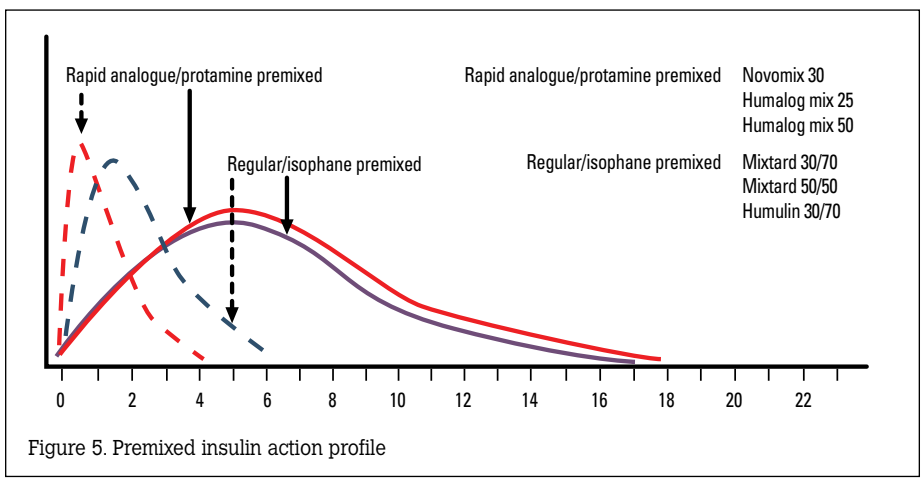


Figure 5. Premixed insulin action profile

Conclusion

The maintenance of near normal glucose levels remains the cornerstone for the management of type 2 diabetes and the prevention of its complications.

Unfortunately, the current evidence suggests that there is significant inertia in intensifying hypoglycaemic therapies, especially the initiation of insulin therapy.[7,8] Insulin should be considered in individuals on maximal tolerated doses of metformin and sulfonylureas who have an HbA1c >7.0% over a 3–6 month period. Current guidelines suggest that insulin therapy can be initiated using basal or premixed preparations. Once insulin is commenced, oral glucose lowering therapies should initially be continued, especially metformin, and a plan needs to be in place for the appropriate adjustment of insulin doses. Although good glucose control is important in preventing the development of diabetes related complications, especially microvascular complications, it needs to be put in the context of a multifactorial approach to the management of diabetes that also targets lipid and blood pressure control. This approach has been shown to result in a reduction in cardiovascular events and mortality in randomised controlled trials.

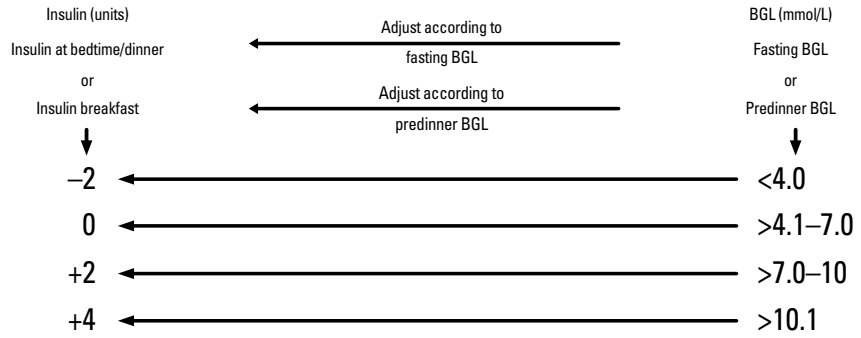


Figure 6. Retrospective adjustment of insulin doses (units) according to BGL

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