Insulin and type 2 diabetes: how and when to start

ROGER CHEN MB BS(Hons), FRACP, PhD

The early introduction of the concept that diabetes is a progressive disease and that escalation of pharmacological therapy is often needed is a useful manoeuvre to assist patients with the initiation of insulin.

Type 2 diabetes is a chronic and complex condition characterised by insulin resistance and progressive pancreatic beta cell deficiency together with other metabolic derangements. Management of hyperglycaemia entails initially not only the use of oral hypoglycaemic medications, such as metformin, but also, importantly, self-management, with appropriate food intake and physical activity.

Traditionally it has been accepted that insulin needs to be commenced when maximally tolerated doses of existing oral hypoglycaemic therapy, usually metformin and a sulfonylurea, fail to maintain adequate glycaemic control.[1,2] Acarbose, thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) antagonists (the gliptins) are second- and third-line oral drug options. The gliptins and the thiazolidinedione pioglitazone are PBS reimbursed for dual therapy (with metformin or a sulfonylurea). Pioglitazone is also reimbursed for triple therapy. The glucagon-like peptide (GLP) agonist exenatide is an alternative second- or third-line drug option in some cases.

There is always debate about the sequence of use of the various hypoglycaemic medications. It could be argued that it matters less which drug or 'pathway' is used, and more that the patient's glycaemic target is reached, as long as there are no contraindications to using the drugs.

The early introduction of the concept that diabetes is a progressive disease and that escalation of pharmacological therapy is often needed is a useful manoeuvre to assist patients with the initiation of insulin. It may be necessary to let patients try triple oral drug therapy as long as there are no contraindications (for example, thiazolidinedione use is contraindicated in

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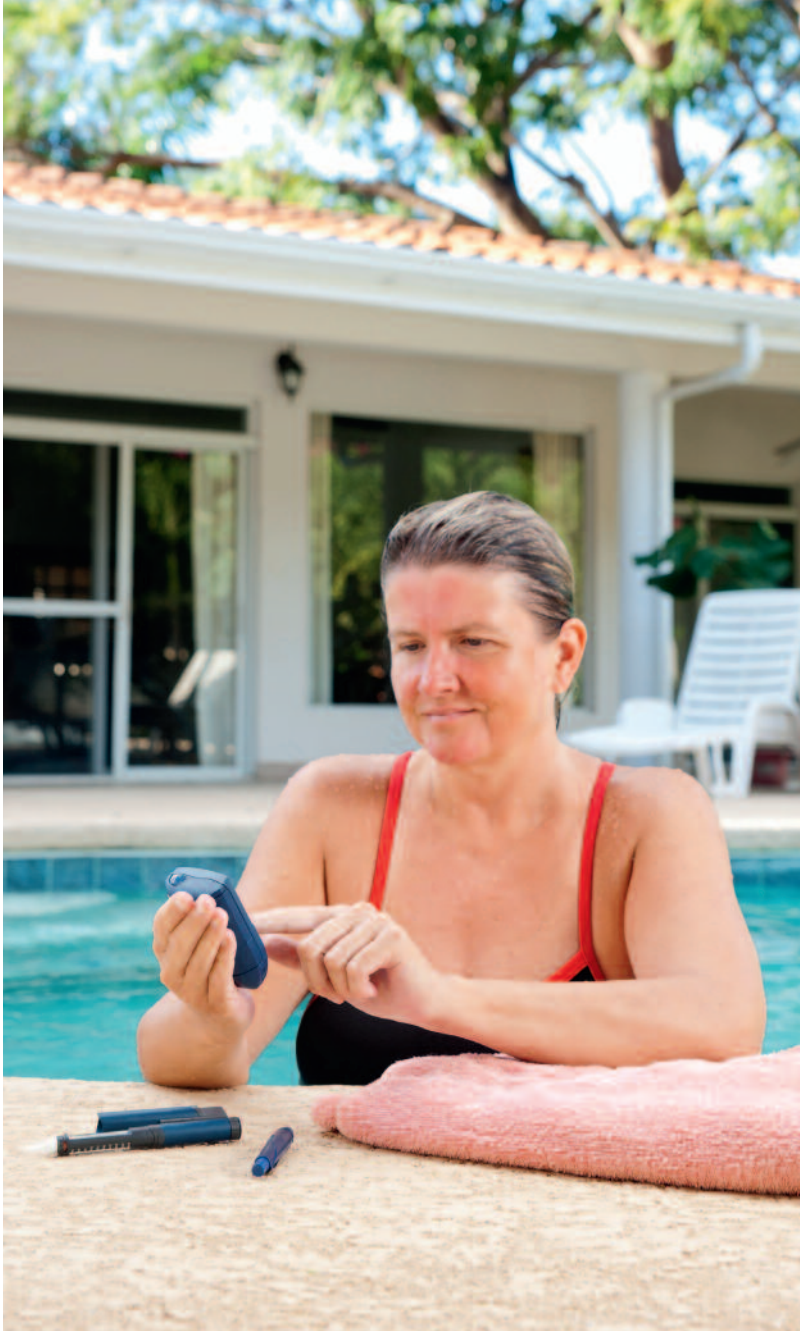
Dr Chen is Senior Staff Specialist in Endocrinology at the Repatriation General Hospital, Concord, Sydney; Clinical Associate Professor in Medicine at the University of Sydney; and an Adjunct Professor at the University of Technology, Sydney, NSW.



Key points

- **Many patients with type 2 diabetes will require insulin.**
- **Basal insulins and premixed insulins can both be effective but the choice of which insulin to use will depend on the pattern of the blood glucose abnormalities.**
- **Patients' blood glucose profile should be reviewed regularly.**
- **The mechanics of insulin administration can be simple but patients should be reviewed by a diabetes educator and dietitian.**

patients with heart failure). This may serve to convince the patient that insulin is indeed necessary. In this situation, it is important not to delay insulin therapy for more than a few months; a trial of triple therapy for three months is sufficient to assess whether it is effective.[3]

This article provides general guidelines and advice about initiating insulin therapy in patients with type 2 diabetes, and also provides several references for further reading.[3-7] It is not within its scope to provide a comprehensive discussion on the topic. The references relate to articles aimed at diabetes management, particularly the initiation of insulin in general practice. The Australian Diabetes Society GP Training Days are another useful resource and provide an excellent and comprehensive forum in which GPs can gain expertise in diabetes management.

When should insulin therapy be started?

There are no unequivocal criteria for when to commence insulin therapy but, in general, it should be considered when a patient's glycosylated haemoglobin (HbA_{1c}) level has been above 7.5% for longer than three to six months and/or where adequate glycaemic

Table 1. Basal human insulins available

Insulin	Trade name	Delivery device types	Onset	Peak	Duration of action
Traditional basal insulin (intermediate-acting)					
Isophane (rbe)	Humulin NPH	Reusable pen (HumaPen), syringe	2 to 4 hours	4 to 8 hours	8 to 12 hours
Isophane (rys)	Protaphane	Reusable pen (Penfill), syringe, large disposable injection device (InnoLet)	2 to 4 hours	4 to 8 hours	8 to 12 hours
Basal insulin analogue (long-acting)					
Glargine	Lantus	Disposable pen (SoloStar), reusable pen (ClikStar), syringe	2 to 4 hours	No peak	20 to 24 hours
Detemir (rys)*	Levemir	Disposable pen (FlexPen), reusable pen (Penfill)	2 to 4 hours	No peak	12 to 18 hours

* Detemir is PBS-subsidised only for use in type 1 diabetes.

Table 2. Premixed insulins available

Insulin	Trade name	Delivery device types	Onset	Peak	Duration of action
Traditional bolus insulin/traditional basal insulin mix (short-acting/intermediate-acting)					
30% Neutral (rys)/ 70% isophane (rys)	Mixtard 30/70	Reusable pen (Penfill), large disposable injection device (InnoLet)	30 to 60 mins	Dual	8 to 12 hours
30% Neutral (rbe)/ 70% isophane (rbe)	Humulin 30/70	Reusable pen (HumaPen), syringe	30 to 60 mins	Dual	8 to 12 hours
50% Neutral (rys)/ 50% isophane (rys)	Mixtard 50/50	Reusable pen (Penfill)	30 to 60 mins	Dual	8 to 12 hours
Bolus insulin analogue/bolus insulin analogue protamine suspension mix (ultra short-acting/intermediate-acting)					
30% Aspart (rys)/ 70% aspart (rys) protamine	Novomix 30	Disposable pen (FlexPen), reusable pen (Penfill)	5 to 15 mins	Dual	8 to 12 hours
25% Lispro (rbe)/ 75% lispro (rbe) protamine	Humalog Mix25	Disposable pen (KwikPen), reusable pen (HumaPen)	5 to 15 mins	Dual	8 to 12 hours
50% Lispro (rbe)/ 50% lispro (rbe) protamine	Humalog Mix50	Disposable pen (KwikPen), reusable pen (HumaPen)	5 to 15 mins	Dual	8 to 12 hours

control has not been achieved. An HbA_{1c} target of 7.0% is generally recommended in most patients, but the Australian Diabetes Society prudently recommends individualisation of targets to a tighter or lesser degree.[8] Higher HbA_{1c} targets are appropriate in elderly patients with comorbidities such as stroke or ischaemic heart disease, and tighter targets are possible in young patients, especially those taking glucose-lowering therapies that have a low risk of causing hypoglycaemia. Early introduction of insulin is likely to be beneficial in the long term even if the patient's HbA_{1c} level is only minimally elevated.

The effect and value of appropriate dietary advice and exercise intervention on metabolic control in every patient cannot be overstated. It is a fallacy to expect glycaemic targets to be achieved with insulin therapy without appropriate dietary advice – insulin is not a substitute for a healthy lifestyle.

How should insulin be started?

Insulins and insulin regimens

Several insulin regimens can be used initially. The NHMRC and International Diabetes Federation (IDF) guidelines appropriately recognise the potential benefits of basal insulins (intermediate-acting and long-acting) and premixed insulins, as does the Diabetes Australia publication *Diabetes Management in General Practice: Guidelines for Type 2 Diabetes, 17th ed, 2011/12*.[1,2,4] The basal and premixed insulins available in Australia are listed in Tables 1 and 2.

When considering which insulin regimen to use, valuable information can be derived from the patient's home blood glucose monitoring rather than depending solely on the HbA_{1c} or pre-breakfast (fasting) blood glucose level readings.

Unlike oral hypoglycaemic therapy, the insulin regimen can be individualised for the patient. The choice of insulin type and the frequency of administration will also be determined by the wishes and ability of the patient. The key to initiating the appropriate insulin regimen and the subsequent adjustment of doses is 'pattern recognition'.

Once the decision has been made to start insulin in a patient, consideration of the checklist in the box on this page can be helpful.

Continuing metformin and sulfonylureas after basal insulin and metformin after premixed insulin has been initiated is generally recommended and is associated with less weight gain and better glycaemic control (i.e. after meals). Sulfonylurea dosages may need to be reduced if there is a risk of hypoglycaemia, and patients initiated on premixed insulin can be weaned off sulfonylureas as glycaemic control improves.

Insulin delivery

Insulins are available as 3 mL cartridges, disposable pens and 10 mL vials. The cartridges can be inserted into reusable insulin pens. Disposable insulin pens incorporate a 3 mL cartridge of insulin. The insulin pens used to deliver insulin are generally simple for patients to learn to use. However, a diabetes educator should revise points 4 to 8 in the checklist (see the box on this page) with the patient to

Initiating insulin: a checklist

1. Determine the patient's blood glucose profile. Is there a consistent pattern?
2. Determine when hyperglycaemia occurs. Is it overnight to morning, universally or after meals only?
3. Use an insulin regimen appropriate to manage the hyperglycaemia that is occurring (point 2).
   If the overnight blood glucose levels are elevated, this regimen may consist of an injection before bed of basal insulin (isophane, glargine or detemir, noting that the latter is not on the PBS for type 2 diabetes). Alternatively, a premixed insulin (usually aspart/aspart protamine or lispro/lispro protamine) can be used at dinner if postprandial glucose levels after dinner and pre-breakfast glucose are elevated. The premixed insulin can be used at breakfast (if blood glucose levels are good before breakfast but rise after breakfast and during the day) or twice daily (if blood glucose levels are universally elevated).
   Less commonly a basal–bolus regimen can be used.
4. Ensure the patient addresses lifestyle factors.
5. Ensure that the patient is aware of the symptoms of hypoglycaemia and knows how to avoid hypoglycaemia and how to treat it should it occur.
6. Revise with the patient the guidelines for sick day management for people with diabetes.
7. Revise with the patient the guidelines for driving with diabetes, including licensing and insurance requirements.
8. Review the patient's progress regularly after insulin initiation, with blood glucose monitoring and titration of insulin as required.
9. In general, metformin can be continued. Sulfonylureas can be continued with basal insulin but dosages may need to be reduced if there is a risk of hypoglycaemia. Sulfonylureas are usually ceased with premixed insulin but are continued in some cases.

Insulin dose adjustment

- Initiate insulin therapy with 6 to 10 units of basal or premixed insulin.
- Adjust the insulin dose in 2- to 4-unit increments/decrements every few days to reach the target fasting blood glucose level (BGL) of 6 mmol/L.

Average BGL (mmol/L) at same timepoint over preceding 2 to 3 days	Insulin decrease/ increase (units)
<4	–2
4.0 to 7.0	0
7.1 to 10.0	+2
>10	+4

- If the pre-breakfast blood glucose value is not at target, adjust the dinnertime or bedtime dose of premix or basal insulin respectively.
- If the daytime or pre-dinner blood glucose value is not at target, adjust the morning dose of insulin.

ensure that the patient's injection technique (including the injection site) is appropriate.

Diabetes educators can also play an invaluable role in teaching the correct technique for the self-injection of insulin.

Monitoring and insulin titration

Once insulin treatment has been initiated, regular review of the patient and his or her blood glucose levels is necessary to aid 'pattern recognition'. Patients often present with daily pre-breakfast blood glucose readings, which can be useful but may not be adequate to make meaningful changes to the insulin dose or regimen, particularly if the HbA_{1c} is still significantly elevated. It is important to try to ensure that the blood glucose monitoring is used as a tool to identify and solve problems, particularly hypoglycaemia and hyperglycaemia, and in conjunction with the HbA_{1c}.

Various titration schedules have been described. Regardless of which schedule is used, the most important consideration is for the patient to be reviewed regularly and frequently with appropriate adjustments to the insulin doses made according to his or her blood glucose profile.

In general, and depending on the patient's blood glucose levels, a dose of six to 10 units of premixed or basal insulin would be appropriate as the initial dose, unless there is significant hyperglycaemia. Usually, insulin can be adjusted in two- to four-unit increments (or decrements) every few days in response to the average blood glucose level at one or more timepoints during the preceding two to three days (see the box on this page). For example, if basal insulin is used at night, one timepoint to use for titration would be the pre-breakfast blood glucose level. If a premixed insulin is used in the morning, the pre-dinner blood glucose level would be used.

Role of the GP

The GP is a key and central part of the management of a patient with diabetes. The inevitable need for insulin therapy in most patients with type 2 diabetes is best discussed early with individual patients, the knowledge that insulin may be necessary facilitating the transition to insulin when this is needed.

Having patients perform practice injections of saline soon after being diagnosed with diabetes and again when insulin therapy is being considered may help them to allay any anxieties about daily injections.

When to refer

GPs will need to initiate insulin therapy in many patients with diabetes. It is important that the patient should have the opportunity to see a diabetes educator during this process. Referral of the patient to an endocrinologist should occur if the HbA_{1c} and blood glucose levels are still elevated despite the initiation and titration of insulin, if there is hypoglycaemia or if the patient is pregnant or planning to conceive (and as early as possible regarding pregnancy).

Conclusion

Insulin is an effective therapy for hyperglycaemia in patients with type 2 diabetes, and there are several effective insulin regimens that can be individualised to suit the patient. However, it is essential that 'lifestyle' factors (an appropriate diet and physical activity) continue to be part of the management of the patient. The GP is central to the management of these patients, and other key members of the multidisciplinary team include a diabetes educator, a dietitian and an endocrinologist. **ET**

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