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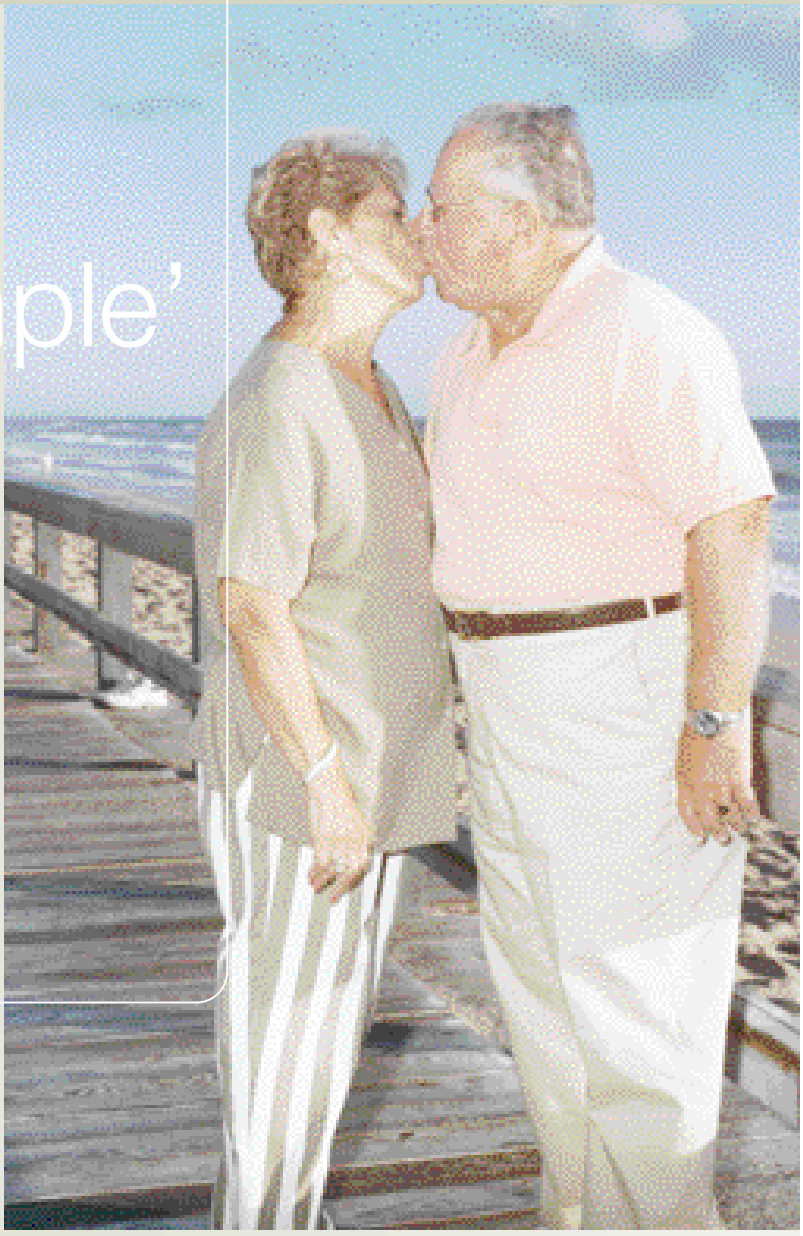
Reprint Collection

KISS: 'keep insulin safe and simple'



Initiating insulin in type 2 diabetes

Living with insulin and type 2 diabetes

Troubleshooting insulin problems in type 2 diabetes

Titrating insulin in type 2 diabetes

Patient handout
How to inject insulin

Patient handout
Insulin therapy and air travel

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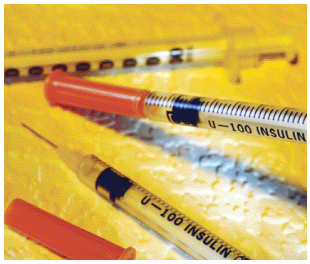

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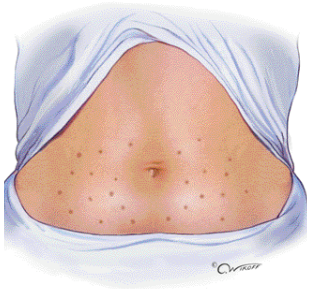
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New developments in the management of type 2 diabetes

There have been several interesting developments in the management of hyperglycaemia in type 2 diabetes since the first edition of this collection of articles in August 2007. The points made in these articles are, however, still relevant, and the articles have not required revision in light of these developments.

The glitazones

A meta-analysis reported a small but statistically significant increase in the risk of myocardial infarction with the use of rosiglitazone. The meta-analysis has been criticised and it is still not clear that rosiglitazone does increase the risk.[1]

The problems of potential drug interactions, delay of several weeks before full therapeutic effect, peripheral oedema and the risk of pulmonary oedema in those patients who have heart failure and are taking rosiglitazone or pioglitazone are well known. However, the following new problems have been identified:

- there is an increased risk of peripheral fractures in women taking rosiglitazone (but not in men)
- there may be an association between taking glitazones and the development or worsening of diabetic macular oedema
- although the incidence of liver toxicity is much lower than with the first available glitazone (troglitazone), both pioglitazone and rosiglitazone have been associated with cases of liver toxicity.

For more information, see the glitazone update published by the National Prescribing Service in the December 2007 issue of *RADAR* (www.npsradar.org.au/npsradar/content/ rosiglitazone. pdf).

The GLP-1 mimetics and enhancers

Two classes of medication now target glucagon-like peptide (GLP-1), which enhances insulin secretion, inhibits glucagon secretion and reduces both fasting and postprandial blood glucose. The GLP-1 'mimetics' are injected medications that bind to the GLP-1 receptor. The 'enhancers' are oral medications and slow the breakdown of endogenous GLP-1. At the time of publication, both the GLP-1 mimetic exenatide (Byetta) and the enhancer sitagliptin (Januvia) are only available on private script.

Both the mimetics and the enhancers have similar efficacy to the other oral hypoglycaemic agents. The mimetics also aid weight loss and the enhancers are weight-neutral.

The main side effects with exenatide are nausea and vomiting, injection site reactions and possibly pancreatitis. Those with sitagliptin are upper respiratory tract symptoms and skin lesions.

ACCORD, ADVANCE and VA Diabetes trials

On 6 February, 2008, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial of intense glycaemic control was stopped because of safety concerns (www.nhlbi.nih.gov/health/prof/heart/other/accord). The study was to compare the outcomes of intense (target A_{1c} value $< 6\%$) and standard ($A_{1c} < 7\%$) glycaemic control. The two arms were associated with median A_{1c} values of 6.4% and 7.5%, respectively, and there was a 20% relative and 0.3% absolute increased risk in mortality in the intensive treatment arm. It is not clear whether this increased mortality was a chance observation or why such an association might occur. Subsequent analysis has shown that the increase in mortality was not associated with hypoglycaemia or any particular drug combination.

On 13 February, one week later, interim findings from the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) Study were released (www.advance-trial.com). This study, comparing intensive and standard glycaemic control (target A_{1c} values $< 6.4\%$ and $< 7\%$, respectively), has shown no increase in mortality with intensive treatment.

The results of a third study, the Veterans Affairs (VA) Diabetes Trial, will be presented at the meeting of the American Diabetes Association in June 2008. It may then become clear if there is an increased risk of mortality with intense glycaemic control and, if so, why it occurs.

Conclusion

The three developments discussed here do not affect the points made in the articles in this KISS supplement. However, the following comments seem reasonable.

- The possibility of a newly identified problem should be considered when prescribing a glitazone.
- The GLP-1 mimetics and enhancers offer a wider choice of hypoglycaemic treatment to those who can afford them.
- Targets for A_{1c} should be individualised and the potential risks as well as the potential benefits of glycaemic control should be considered. MT

Reference

1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356: 2457-2471.

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KISS: 'keep insulin safe and simple'

Starting patients on insulin therapy and managing them on this treatment are made more straightforward following the guidelines given in this collection of articles from past issues of Medicine Today.

PAT J. PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)

Two insulin-related problems are associated with type 2 diabetes: progressively increasing insulin resistance and progressively decreasing insulin secretion capacity. At diagnosis, beta cell function is about 50% of normal; thereafter, it progressively decreases by 3 to 4% per year. It is no surprise that insulin therapy will eventually be needed in many patients with type 2 diabetes. Furthermore, as the beta cell function decreases then the insulin dose needs to progressively increase to maintain glycaemic control.

The number of Australians with type 2 diabetes has doubled in the past 20 years. The vast majority of these patients are managed by GPs, and it is these GPs who will decide when and how to start insulin. The reasons for starting insulin sooner rather than later are quite clear:

- the Diabetes Control and Complications Trial (DCCT; carried out in patients with type 1 diabetes) and the United Kingdom Prospective Diabetes Study (UKPDS; in type 2 diabetes) established A_{1c} as the 'gold standard' index of glycaemic control with a clear relation to long term microvascular diabetic complications[1,2]
- national guidelines in Australia recommend measurement of A_{1c} in patients with type 2 diabetes at least annually[3]
- in Australia, the evidence based recommended target value for A_{1c} is below 7%[3]
- the UKPDS found that approximately 50% of patients newly diagnosed with type 2 diabetes required insulin therapy within six years to maintain A_{1c} below 7%[4]
- approximately 40% of Australians with type 2 diabetes have an A_{1c} above 7%[5]
- the Western Australian Fremantle Diabetes Study showed that A_{1c} values at the transition from oral hypoglycaemic agents to insulin were above A_{1c} values at the transition from lifestyle to oral hypoglycaemic agents (9.4 and 7.7%, respectively)[6]
- the evidence based recommended starting schedule for insulin in patients with type 2 diabetes is bedtime basal insulin (intermediate acting isophane insulin) with continuation of oral hypoglycaemic agents[7]
- there are consensus recommendations for titrating insulin therapy for type 2 diabetes.[8]

Just as resistance and capacity factors – resistance to insulin and capacity of insulin secretion – cause the progression of type 2 diabetes, similar factors may cause delay in initiation of insulin therapy – psychological resistance on the part of the patients and doctors and lack of capacity in healthcare systems. While the problems of starting insulin are immediate and obvious to both doctors and patients, the problems of not starting are more remote and less perceptible – i.e. a progressive increase in the risk of diabetes-related complications.

Starting insulin is not hard, not risky and does work. The first step is to get the preprandial blood glucose levels (BGLs) on target: start with breakfast and then move on to the evening meal. Once these are controlled, check that the BGLs in the middle of the day and the evening are also controlled. To make sure glycaemia is on target around the clock, check the A_{1c} six to eight weeks after all the BGLs are on target.

Insulin is your friend

This *Medicine Today* Reprint Collection includes guidelines on starting, troubleshooting and titrating insulin in patients with type 2 diabetes. These guidelines can be summarised by the following jingle:

'First fix the fasting
Then tackle tea
Find the hidden hypers
And check the A_{1c}'

Next time you see a patient who is on maximum oral hypoglycaemic therapy and has an A_{1c} above 7%, start him or her on insulin using the KISS guide. Both you and your patient will feel much better. Remember, 'insulin is your friend'. MT

Dr Phillips is Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

References

See page 27 for references 1 to 8.

MedicineToday PEER REVIEWED ARTICLE
MedicineToday 2007; 8(3): 23-34
Updated May 2008

KISS: 'keep insulin safe and simple'

Part 1: initiating insulin in type 2 diabetes

Lifestyle change and oral hypoglycaemic agents will initially be effective in achieving stable and on-target blood glucose levels in patients with type 2 diabetes. However, the time will come when insulin therapy has to be started.

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Many patients with type 2 diabetes eventually require insulin therapy for glycaemic control. While the problems of starting insulin are immediate and obvious to both doctors and patients, the problems of not starting are more remote and less perceptible – a progressive increase in the risk of diabetes related complications. However, starting insulin is not hard, not risky and does work.

This article provides a simple six-step guide to starting insulin therapy in patients with type 2 diabetes to achieve stable and on-target blood glucose levels (BGL). The accompanying patient handout provides a guide to the procedure of injection insulin (see pages 35 to 38).

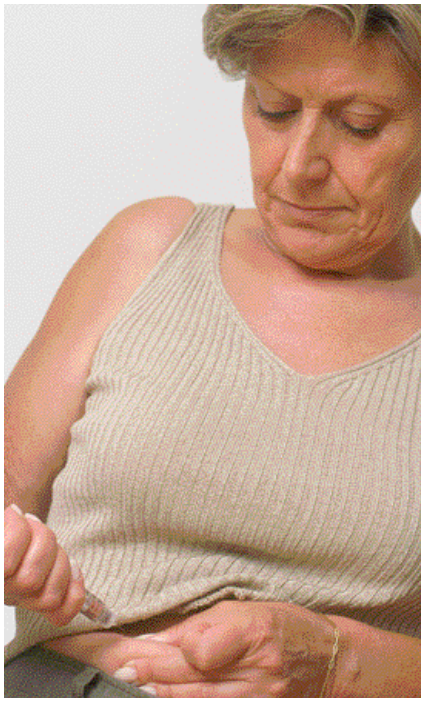
Step 1. Is the patient's A_{1c} on target?

Individual glycosylated haemoglobin (A_{1c}) targets will depend on the likelihood of microvascular complications and problems with insulin. However, the United Kingdom Prospective Diabetes Study (UKPDS) has shown that the higher the A_{1c} then the greater the microvascular risks.[1] Usually an A_{1c} above 7% (BGL above 8 mmol/L) and certainly an A_{1c} above 8% (BGL above 10 mmol/L)

IN SUMMARY

- **An A_{1c} above 7% (BGL above 8 mmol/L) and certainly an A_{1c} above 8% (BGL above 10 mmol/L) should prompt consideration of starting insulin therapy.**
- **Before starting insulin check the patient's lifestyle, adherence to diabetes medications, the presence of other conditions and the other medications prescribed.**
- **Choosing the type of basal insulin depends on the pros and cons of the intermediate acting isophane insulin and the long acting insulin analogue and the patient's choice of injection device. If the fasting BGL is high, the insulin should be used at bedtime; if the fasting BGL is on target but the evening BGL is high, the insulin should be used in the morning. The starting dose should be 10 units.**
- **When adjusting basal insulin, approach targets fast and fine tune slowly. 'Going slow' can take too long; 'going fast' can cause hypoglycaemia and weight gain.**
- **Once basal insulin and preprandial blood glucose are on target consider stopping oral hypoglycaemic agents, particularly sulfonylureas, and consider starting quick acting insulin before meals.**
- **Potential problems starting insulin include coping with practical details, hypoglycaemia, weight gain and psychological resistance.**

continued



PHOTOLIBRARY

Table 1. Secondary causes of hyperglycaemia*

Medications

Oral contraceptive pill
Oral corticosteroids
Thiazides
Beta blockers
Phenytoin
Antipsychotics
Glucosamine

Medical conditions

Urinary tract infections (including those that are asymptomatic)
Dental infections (including those that are asymptomatic)
Hyperthyroidism
Occult malignancy

* Not an exhaustive list.

should prompt action.[2]

Some people think that the A_{1c} and blood glucose 'numbers' give comparable assessments of glycaemic control – e.g. an A_{1c} of 8% corresponds to an average BGL of 8 mmol/L. Some also think '5 to 10' is okay for both numbers. However, this is not so.

The A_{1c} value reflects the overall average BGL (24 hours per day over several weeks). Within the ideal ranges for both A_{1c} and BGL, values do approximate each other, but at higher than ideal levels, the A_{1c} value is lower than the average BGL, with the difference between the two increasing with increasing values.[3] The formal relation between BGL and A_{1c} can be described by the equation:

$$BGL\ (mmol/L) = 2A_{1c}(\%) - 6$$

where BGL is the average over 24 hours.

Following this formula, an A_{1c} of 8% equates to a BGL of 10 mmol/L.

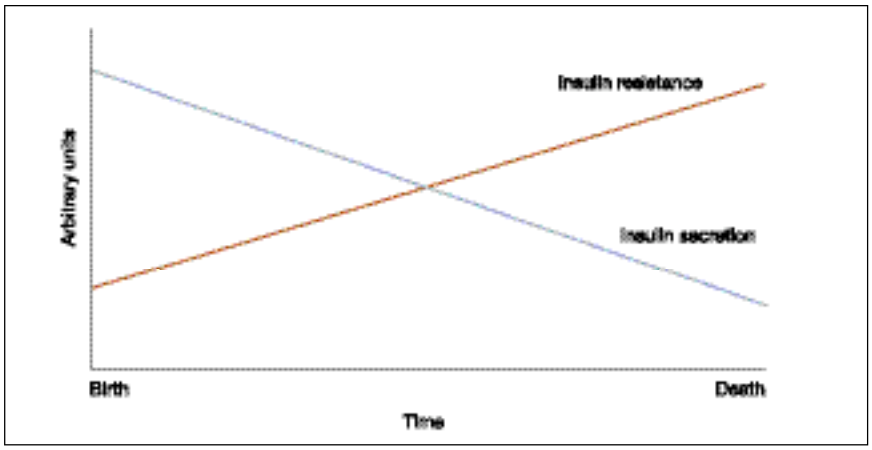


Figure 1. Diabetes progression – insulin resistance and insulin capacity. With progression of disease the capacity of beta cells to secrete insulin and the body's capacity to respond to insulin both decrease. Prediabetes (impaired fasting glucose, impaired glucose tolerance) starts when insulin resistance exceeds insulin secretory capacity (point of intersection). Diabetes progressively worsens with time.

Step 2. Are there potential lifestyle or medication changes, or treatable medical conditions?

Lifestyle

There are two very practical reasons to check lifestyle:

- insulin therapy will not substitute for a healthy lifestyle – starting insulin in people who are overweight, underactive or overeating is likely to increase their weight and may not improve blood glucose control
- many patients gain weight when starting insulin – partly because controlling glycaemia controls glycosuria, thus increasing the amount of glucose available in the body.

Patients considering insulin should be encouraged to 'eat less and walk more',[4] but lifestyle change should not become a reason for the person (and doctor) to delay insulin.

Medication adherence

Most doctors know that many patients do not take their medication as prescribed. We sometimes forget, however, that *our* patients may not perfectly adhere to the treatment schedule we prescribe.

Consider making the comment: 'One reason for your high A_{1c} value could be that you are not getting enough tablets. Most patients forget to take some of their tablets – how often do you miss yours?'

Also consider reviewing the patient's overall medication schedule. Aim for a once or twice daily dosing schedule and a lower number of tablets to be taken (by using higher tablet strengths and combined formulations).

Doctors also sometimes forget to

Table 2. Characteristics of basal insulins

Insulin type	Trade name	Origin	Appearance	Comments
Intermediate acting				
Isophane	Humulin NPH	Human	Cloudy	Available as vials for use in syringes and cartridges for use in pen injectors
	Protaphane	Human	Cloudy	Available as vials for use in syringes, cartridges for use in pen injectors, disposable pen injectors and a larger disposable injection delivery device (InnoLet)
Long acting				
Detemir	Levemir	Analogue	Clear	Available as cartridges for use in pen injectors and disposable pen injectors
Glargine	Lantus	Analogue	Clear	Available as vials for use in syringes, cartridges for use in pen injectors and disposable pen injectors

increase doses of prescribed oral hypoglycaemic agents or add extra medications to keep the A_{1c} on target. The usual sequence of oral hypoglycaemic agents is: lifestyle +/- metformin +/- sulfonylurea +/- glitazone. At present, rosiglitazone (either as a single agent formulation [Avandia] or combined with metformin [Avandamet]), is eligible for PBS subsidy as dual and triple therapy (i.e. with metformin and/or a sulfonylurea). Pioglitazone (Actos) is only eligible for PBS subsidy as dual therapy (i.e. with metformin or a sulfonylurea).

Remember though that as type 2 diabetes progresses, the component of insulin deficiency becomes more and more important (Figure 1). Neither insulin secretagogues (sulfonylureas and glitinides) nor sensitisers (glitazones and, to a lesser extent, metformin) will work if there is insufficient insulin.

As for lifestyle change, medication change should not delay initiation of insulin therapy if a patient's A_{1c} value remains above target.

Other medications and medical conditions

Before starting a patient on insulin check that he or she is not taking a medication or has a medical condition that can cause hyperglycaemia (Table 1). Although it may not be possible to change a secondary cause, or changing it may not result in A_{1c} targets being met, it is worth trying.

Step 3. Which basal insulin and which injection device?

In general, once daily basal insulin plus continuing oral hypoglycaemic agents is preferred over other schedules (twice daily basal, basal/bolus, premixed insulin; stopping oral hypoglycaemic agents) because glycaemic control is better and weight gain and hypoglycaemia are less.[5]

There are two types of basal insulin (Table 2):[2]

- the intermediate acting isophane insulin (Humulin NPH, Protaphane), which is cloudy in appearance
- the long acting analogue insulins detemir (Levemir) and glargine (Lantus), which are clear.

Both isophane and analogue insulins will do the job but each has its pros and cons (Table 3).[6] Both analogues are subsidised by the PBS to treat type 1 diabetes. Currently, glargine is subsidised by the PBS for all forms of insulin therapy in type 2 diabetes, and detemir is TGA-approved but not PBS-subsidised for use in type 2 diabetes.

In some patients, the choice of injection device will determine the insulin prescribed. Some patients prefer a particular brand of reusable insulin pen injector,

Table 3. Basal insulins – pros and cons of analogue compared to isophane insulin

Pros

Consistent profile
Often single daily dose
Less hypoglycaemia than with isophane insulin
No mixing or resuspension needed for injection

Cons

Slower response to dose changes than with isophane insulin
May be confused with bolus insulins as both are clear solutions
Cannot mix with bolus insulins*
Glargine may sting when injected

* Little data on safety or efficacy available.

Basal insulin titration*

Start with 10 units of basal insulin.
Adjust the dose twice weekly, to reach the target fasting blood glucose of <6 mmol/L, using the guidelines below:

Mean fasting glucose over preceding 2 days (mmol/L)	Insulin increase (U/day)
>10	8
8 to 10.0	6
7 to 7.9	4
6 to 6.9	2

- Do not increase the insulin dose if the fasting blood glucose level is <4 mmol/L at any time in the preceding week.
- The insulin dose may be decreased (small decreases of 2 to 4 units) if there is severe hypoglycaemia (requiring assistance) or the blood glucose level is <3.0 mmol/L in the preceding week.

* Adapted from reference 7 (*Diabetes Care* 2003; 26: 3080-3086).

and the use of insulin cartridges of a different brand is not recommended. Other patients prefer the convenience of disposable insulin pen injectors or the traditional insulin syringe. Finally, some find the syringes and the fountain pen-like injectors difficult to use and prefer a larger device (InnoLet) where the dose is easily adjusted, the numbers are larger, the device is easier to grasp and the plunger is easily depressed.

While in type 1 diabetes, the flatter profile, longer action and more consistent absorption profile often make analogue basal insulins the better choice, in type 2 diabetes both isophane and the analogue basal insulins are suitable. Whichever basal insulin is chosen, the time of dosage depends on the blood glucose profile. Usually the fasting BGL is high and a bedtime dose is appropriate to control the overnight liver glucose output that causes fasting hyperglycaemia. However, sometimes the fasting BGL is on target but the evening preprandial BGL is high, suggesting that a morning dose is needed.

Having decided the injection device, the type of basal insulin and the timing of the delivery, choosing the initiating dose is easy: start with 10 units.

Step 4. How should the basal insulin dose be adjusted?

Adjusting the basal insulin dose slowly could mean it would take many months to achieve optimal control. For example, it could take 15 months or more for those patients needing 50 to 100 units of basal insulin per day if the dose was increased by 2 units every two weeks from the starting dose of 10 units – both you and the patient would have given up by then.

However, increasing the dose too fast may cause hypoglycaemia and weight gain. The last thing you want for an apprehensive patient (and family) is to cause hypoglycaemia and/or dramatic weight gain because of excess hunger.

The answer is *festina lente* – hasten slowly. An example of an appropriate insulin titration protocol is given in the box on this page. The principles are:[7]

- when blood glucose is well above target, increase by larger amounts than when blood glucose is close to target
- adjust doses every two to three days; even better, encourage the patient to change the dose following an agreed protocol, perhaps with advice from your practice nurse.

Note that the BGL target in the example protocol can be changed, with corresponding changes in the dosage adjustment.

Following such an insulin titration protocol will enable targets to be achieved more quickly than going slowly (in our example, eight to 12 weeks rather than 15 months) but with less risk of hypoglycaemia and weight gain than going fast.

Once the fasting preprandial BGL is on target, check the other (the evening) preprandial BGL. For those patients who have fasting BGL on target but high evening BGL, once the evening preprandial BGL is on target, check the fasting preprandial BGL. In both instances, if the other preprandial BGL is not on target then add a second dose of basal insulin (10 units) and adjust according to the agreed protocol to achieve target preprandial blood glucose control.

Step 5. Should oral hypoglycaemic agents be stopped and/or quick acting bolus insulin started?

Should oral hypoglycaemic agents be stopped?

Stopping an oral hypoglycaemic agent would mean fewer tablets to be taken but may also mean that the daily insulin dose would have to be increased or a second dose added. The sulfonylurea may no longer be able to increase insulin secretion. The insulin sensitisers will continue to work since insulin resistance remains a problem, but the risk of serious side effects progressively increases with the patient's age and the duration of diabetes (with metformin, lactic acidosis; with the glitazones, fluid overload and cardiac failure).

What is the patient's A_{1c}?

A_{1c} values reflect BGLs over the past few weeks and therefore provide a check that

a patient's BGL records are giving an accurate view of overall blood glucose control.

The target A_{1c} value can usually be achieved using a bedtime and/or morning basal insulin dose with or without metformin or a glitazone. If a patient's A_{1c} is not on target with this schedule, check the following items.

- **The patient's reported blood glucose results are accurate.** If the patient's average BGL is very different from that predicted by the A_{1c} (the average BGL should be $2A_{1c} - 6$, as mentioned earlier) then his or her blood glucose measurements and/or records may not be accurate or adequate.

Blood glucose results may be misleading because the glucose meter, glucose strip or patient technique is faulty. Patients may not be conducting regular quality control checks to ensure that their technique is accurate, and they may be getting incorrect high or low readings. Occasionally patients do not record high or low values because they 'know what caused them' and 'it was an unusual event'. Rarely, patients will enter incorrect results or results of nonexistent tests. This may be to give a 'good' report to the doctor because the doctor clearly wants certain tests to be done and certain results to be obtained.

- **The patient's BGL results are similar to laboratory results.** Compare the laboratory BGL measurement of a fasting blood sample against the patient's BGL measurements immediately before and after the blood is taken. This will give an idea of the variability between the patient's values and between the mean of the patient's values and the actual (laboratory) value.
- **The reported A_{1c} results accurately reflect glycaemia.** Ask the laboratory if there is a possibility that their A_{1c} assay is giving misleading results (e.g. with a haemoglobinopathy or uraemia). Ask yourself if red blood cell turnover could be increased (due to, for example, haemolysis or blood loss) as the A_{1c} value depends on the average BGL during the lifetime of the red cell.
- **There is no 'hidden hyperglycaemia'.** Assuming reported blood glucose and A_{1c} values are accurate, preprandial BGLs are on target and A_{1c} is off target, check postprandially and during the night (at, for example, 3.00 a.m.) for 'hidden hyperglycaemia'. Usually discrepancies between preprandial BGL and A_{1c} can be resolved but occasionally hyperglycaemia can 'hide' postprandially and/or during the night.

Review BGLs before lunch and before bedtime to check for morning and evening postprandial glycaemia. Postprandial hyperglycaemia should prompt review of the amount and glycaemic index of the food eaten at that meal (i.e. the glycaemic load).[8] A dietitian will be able to advise on the glycaemic load and on strategies to reduce postprandial glycaemia.

If changes in carbohydrate intake are not needed, practical or effective, then quick acting insulin, in addition to basal insulin, should be considered.

Even if fasting glycaemia is under control, night-time glycaemia can occur because the evening basal isophane insulin dose is given too early. For example, a basal insulin dose with the evening meal at 5.00 p.m. may not provide enough insulin next morning before a late breakfast at 9.00 a.m. Shifting the insulin dose to bedtime may control both BGL and A_{1c}. This is less of a problem with the longer acting analogue basal insulins.

Table 4. Characteristics of bolus insulins

Insulin type	Trade name	Origin	Appearance	Comments
Rapid acting (also known as very quick acting)*				
Insulin aspart	NovoRapid	Analogue	Clear	Available as vials for use in syringes, cartridges for use in pen injectors and as disposable pen injectors
Insulin lispro	Humalog	Analogue	Clear	Available as vials for use in syringes and cartridges for use in pen injectors
Insulin glulisine	Apidra	Analogue	Clear	Available as disposable pen injectors
Short acting (also known as quick acting)†				
Neutral insulin	Actrapid	Human	Clear	Available as vials for use in syringes and cartridges for use in pen injectors
	Humulin R	Human	Clear	Available as vials for use in syringes and cartridges for use in pen injectors

* Onset, 5 to 15 minutes; peak, 30 to 90 minutes; duration, 4 to 6 hours. † Onset, 30 to 60 minutes; peak 2 to 3 hours; duration, 8 to 10 hours.

Table 5. Bolus insulins – pros and cons of analogue compared to neutral insulin

Pros

Inject when eat

Less hypoglycaemia than with neutral insulin

Better postprandial glycaemic control than with neutral insulin

Cons

Need to eat promptly after injection

Possible insulin 'run out' before next meal

Need adequate carbohydrate in meal

Which quick acting bolus insulin is appropriate?

A quick acting bolus insulin should be considered if preprandial BGLs are on target but A_{1c} and postprandial BGL are not.

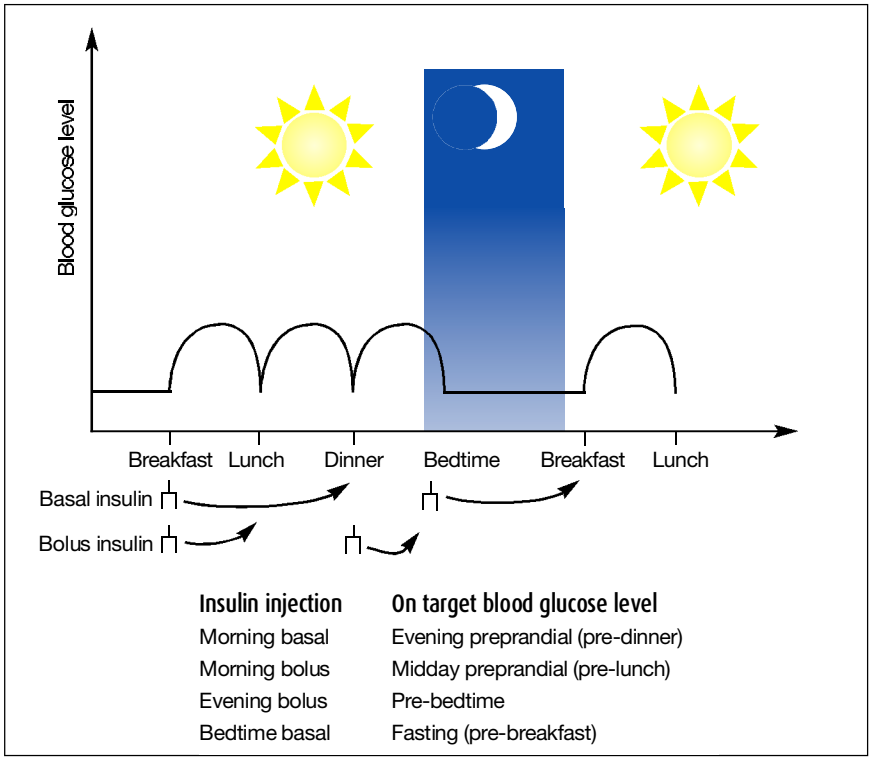
As for basal insulins, there are traditional and analogue bolus insulins (Table 4):

- the rapid acting (or very quick) analogue insulins aspart (NovoRapid), lispro (Humalog) and glulisine (Apidra)
- the short (or quick) acting neutral insulin (Actrapid, Humulin R).

Both analogue and neutral insulins are clear solutions but each has its pros and cons (Table 5). A neutral (human) bolus insulin may act too slowly to control postprandial hyperglycaemia and may act for so long that hypoglycaemia before the next meal becomes a risk. Analogue bolus insulins are faster in starting and stopping, and may control postprandial hyperglycaemia with lesser risk of hypoglycaemia before the next meal. However, the analogues may increase the risk of hypoglycaemia if the meal is not eaten promptly or if enough carbohydrate is not eaten with the meal (the Australian steak and salad is a classic for hypoglycaemia as it contains no carbohydrate). The rapid acting insulin analogues may also 'run out' before the next meal, causing preprandial hyperglycaemia.

Again the choice may be determined by the choice of basal insulin injection device and insulin. The patient may choose the same type of injection device for convenience, but it should be made clear which device has which insulin. Remember that both basal and bolus insulins can be clear and that the pen injectors for both clear insulins may be confused if they are not different brands and/or colours.

For patients on isophane basal insulin, quick acting analogue bolus insulin may control postprandial blood glucose and the isophane insulin control blood glucose before the next meal. For patients on analogue basal insulin, neutral (human) bolus insulin may be better to control the blood glucose before the next meal (especially if the next meal is more than 6 hours after the bolus insulin, when an analogue might 'run out').



Insulin injection	On target blood glucose level
Morning basal	Evening preprandial (pre-dinner)
Morning bolus	Midday preprandial (pre-lunch)
Evening bolus	Pre-bedtime
Bedtime basal	Fasting (pre-breakfast)

Figure 2. Blood glucose profile on basal plus bolus insulin schedule.

What dose of bolus insulin to use?

As with the basal insulin, choosing the initiating dose of bolus insulin is easy: use one-third of the corresponding morning or evening basal insulin dose. The usual recipe is two-thirds basal insulin and one-third bolus insulin.

Adjust the starting dose according to the blood glucose profile. *Festina lente* still applies – not too slow and not too fast, get it 'just right'. Increase the dose by 20% if BGLs are well off target and by 10% when they are closer to target. Figure 2 shows which BGL through the day is controlled by which type of insulin.

Don't aim too low. The major side effect of quick acting insulin is hypoglycaemia (and weight gain because of the associated hunger symptoms). Hypoglycaemia is less likely in patients with type 2 diabetes than in those

Table 6. Causes of psychological insulin resistance

Patients

Insulin therapy will be painful and difficult
Fear of weight gain and hypoglycaemic episodes
'End of the road', diabetes worse
Employment, dependency

Doctors

Patients do not want insulin therapy
Difficult, extra time needed
Patients need referrals
Hypoglycaemic episodes, weight gain
Insulin therapy will not work and is costly

with type 1 diabetes, but can still be a problem with both quick acting and basal insulins.

Step 6. Are problems with insulin likely?

There are two classes of potential problems:[9]

- medical – coping with injection and monitoring techniques (both the patient and the doctor) and risk of hypoglycaemia and weight gain (patient)
- psychological (both the patient and the doctor).

Medical problems

There are very few patients who cannot manage to administer their own insulin or monitor their BGL using the insulin injectors and blood glucose meters available now. For these few, a relative, carer or visiting nurse could help. The basal insulin injection and the preprandial blood glucose measurement are the most important daily activities.

The timing of the basal insulin is often not critical, particularly for the long acting insulin analogues, as long as the dose is given at approximately the same time each day. Blood glucose testing is most important when starting insulin and, for safety, should be determined several times each day when insulin therapy is being initiated.

Initially BGL targets will not be too ambitious (e.g. preprandial targets of 8 mmol/L). Long term monitoring can be by measuring A_{1c} and the occasional preprandial BGL.

Once doctors are convinced that starting insulin is safe and simple, most can refer patients to a nurse experienced in diabetes care who can help the patient choose and use an appropriate insulin injection device and can check blood glucose monitoring technique. If such a nurse is not available, an approach is to

Six steps to initiating insulin therapy for type 2 diabetes

The KISS – or 'Keep insulin safe and simple' – approach involves the six steps to stable sugars outlined below.

Before starting a patient with type 2 diabetes on insulin

- Step 1. A_{1c} levels indicating insulin therapy
  - If A_{1c} >7% (which indicates average blood glucose level (BGL) >8 mmol/L), consider starting insulin.
  - If A_{1c} >8% (which indicates average BGL >10 mmol/L), strongly consider starting insulin.
- Step 2. Making lifestyle or medication changes, and treating other medical conditions

  Check whether making lifestyle or medication changes or treating other medical conditions might get the patient's A_{1c} closer to target; insulin may still be necessary.

When starting a patient with type 2 diabetes on insulin

- Step 3. Selecting the basal insulin and the injection device
  - Choose between isophane or analogue insulin.
  - Choose between syringe, pen or other injector.
- Step 4. Adjusting the basal insulin dose
  - Start with 10 units at bedtime if fasting BGL is high, or 10 units in the morning if fasting BGL is on target but evening preprandial BGL is high.
  - Increase doses every two to three days using agreed protocol.
  - Consider adding a second basal insulin dose if the other preprandial BGL remains high.
- Step 5. Stopping oral hypoglycaemic agents and/or starting quick acting bolus insulin
  - Consider stopping sulfonylurea and decreasing metformin and/or glitazone dose(s).
  - If preprandial BGLs are on target and A_{1c} is high, check that BGL and A_{1c} measurements are accurate and for 'hidden' hyperglycaemia.
  - Consider starting quick acting bolus insulin if preprandial BGLs are on target but A_{1c} and postprandial BGL are not. Use a neutral or analogue bolus insulin; start with one-third of the corresponding morning or bedtime basal dose and increase by 10 to 20% depending on closeness to BGL target.
- Step 6. Coping with potential problems when starting insulin
  - Educate the patient regarding injection technique and blood glucose monitoring and how to cope with hypoglycaemia and weight gain.
  - Discuss psychological insulin resistance with the patient.

Remember: 'Insulin works, insulin is good, insulin is your friend'.

choose one basal insulin preparation and injection device and arrange for a nurse in the practice, hospital or community to become familiar with them. A relevant pharmaceutical representative may be prepared to visit the area and teach the nurse (or the doctor). A similar approach could be adopted when bolus insulin before meals is required. Such a system might take some time to set up but it will enable you and your patients to start insulin simply, safely and sooner.

Psychological problems

As noted, the progressive rise of A_{1c} is caused by defects in insulin resistance and insulin capacity. Often the 'failure' to meet A_{1c} targets is also explained by resistance and capacity factors: psychological resistance on the part of the patients and doctors, and lack of capacity in healthcare systems.[9,10] These lead to delay in starting insulin therapy.

A patient says, 'Just one more try, doctor – I know my blood glucose has been high over Christmas but my New Year's resolution is to lose the 2 kg I gained over the festive season and get back to my regular walks. My wife wants to start walking too and we'll keep each other motivated.' You think, 'Thank goodness, I really didn't want to start insulin right now. The waiting room is packed, I really need to get away soon and I could do without writing scripts, referrals and all the rest of the paraphernalia. However, I must dig out those notes I made so I know which insulin to use and what dose to start with next time it comes up'.

Both patient and physician are showing the psychological insulin resistance that stops or delays people starting insulin (Table 6). Neither wants to take the next step; the problems of starting insulin are immediate and obvious to both. The problems of not starting are more remote and less obvious – a progressive increase in the risk of diabetes related complications.

Many patients and their healthcare providers prefer to delay insulin therapy until it is 'absolutely essential'. However, some of the concerns can be easily resolved, for example:

- demonstrate that injections are virtually painless with a 'dry' injection
- introduce the person to a successful patient
- explain that the risk of hypoglycaemia is remote (1/20th that in type 1 diabetes)[9]
- explain that 'eating less and walking more' will limit or prevent weight gain.[4]

Some concerns are less easy to resolve: some employers do discriminate against people with diabetes (even though this is illegal), and access to some jobs is more difficult for those with diabetes (e.g. airline pilots and the active armed forces). Overall, though, insulin does not limit opportunity much.

Conclusion

Doctors should 'just do it!' Nothing is so persuasive as seeing that starting insulin is not hard, not risky and does work.

The KISS approach – summarised in the box on page 11 – really does work. Most patients (and their doctors) will feel better and wonder why they didn't start insulin much earlier. A patient might say, 'I feel great. I have more energy and don't need daytime naps. If I had known how easy it was to start insulin, I would have done it years ago'. A doctor might say, 'But I thought you had to use a basal bolus schedule with four shots a day. I had no idea how to start, which insulin to use and what doses'.

Remember 'Insulin works, insulin is good, insulin is your friend'.[11] MT

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KISS: 'keep insulin safe and simple'

Part 2: living with insulin and type 2 diabetes

Living with insulin and type 2 diabetes 24 hours a day, seven days a week, can be associated with problems if they are not anticipated and avoided.

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Starting insulin therapy in patients with type 2 diabetes using the KISS approach ('Keeping Insulin Safe and Simple') is not risky, not hard and does work – see the article on initiating insulin therapy on pages 5 to 12 (originally published in *Medicine Today*, March 2007).[1] However, problems can arise when patients are living with insulin and type 2 diabetes 24 hours a day, seven days a week, if these are not anticipated and avoided.

This article considers the common problems experienced by people taking insulin and gives practical advice on how to make living with insulin safe and simple.

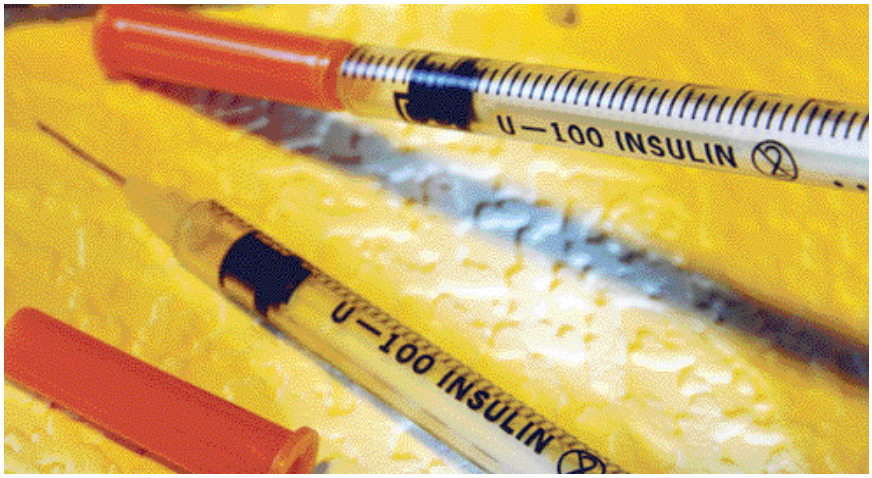
Weight gain

'In the last eight months I've put on 10 kg. I've tried everything but my weight is like an old TAA (Trans Australian Airlines) flight and going 'up, up and away'. You have got to do something to help me.'

Sue is 54 years old and justifiably worried.

IN SUMMARY

- **Continuing oral hypoglycaemic agents and adding 10 units of basal insulin at bedtime is almost always the best way to start insulin in people with type 2 diabetes. Metformin also helps with weight control.**
- **Patients should 'eat less and walk more' to balance the extra energy available when improved glycaemia reduces glycosuria.**
- **Insulin should be adjusted to fit lifestyle, not vice versa.**
- **Improving glycaemic control comes with the price of hypoglycaemia, weight gain and extra effort by patient and doctor.**
- **Blood glucose measurement results may vary by plus or minus 20%, even after the patient's technique and the testing equipment have been checked.**
- **Eating before physical activity reduces the risk of hypoglycaemia and blunts postprandial hyperglycaemia.**
- **When travelling by air, patients should adjust insulin dosages if the time zone difference between origin and destination is more than four hours. Less insulin is needed for travel eastwards (a shorter day) and more insulin for travel westwards (a longer day).**
- **Patients should carry a full set of diabetes equipment in their hand luggage when flying. Taking a survival kit in the hand luggage and a second full set of diabetes equipment in the check-in luggage is recommended. Airline regulations on the carriage of diabetes equipment should be checked.**



When she started insulin eight months ago, she was slightly overweight at 66 kg (height, 156 cm; BMI, 27.1 kg/m^2). Now she weighs 74 kg, her triglyceride level has increased from 1.5 to 3.2 mmol/L and her blood pressure has also increased despite her taking a higher dosage of ACE inhibitor and adding a low dose thiazide.

Table 1. Weight gain in type 2 diabetes[2]

- Improved glycaemic control – leads to decreased glycosuria and weight gain (2 kg per 1% decrease in A_{1c})
- Prandial boluses – lead to weight gain independent of glycaemia
- Oral hypoglycaemic agents, sulfonylureas and glitazones, cause weight gain but stopping them and/or metformin is likely to worsen glycaemia
- Use of premixed insulins – hypoglycaemia caused by the short acting component may lead to weight gain
- Overuse of insulin – may cause hypoglycaemia, increased appetite and weight gain

Why has Sue gained weight?

Sue may have developed a medical condition (such as hypothyroidism) or be taking a medication (such as a tricyclic antidepressant) that is causing her to gain weight. Most likely, however, her increased weight has been caused by:

- using the wrong insulin preparation
- stopping her metformin
- not anticipating weight gain with improved glycaemic control (Table 1)[2].

The wrong insulin

Usually the most appropriate starting insulin schedule is to continue oral hypoglycaemic agents and add a bedtime dose of basal insulin – either intermediate acting isophane insulin (Humulin NPH, Protaphane) or long acting analogue insulin.[3,4] Occasionally, the fasting blood glucose level (BGL) will be on target but the BGL before the evening meal will be high: then a morning dose of basal insulin will be appropriate. Starting with a bedtime basal insulin and continuing oral hypoglycaemic agents produces better glycaemic control, less weight gain and less hypoglycaemia than other insulin schedules (twice daily basal, basal/ bolus, twice daily premix), and only needs one injection.[4]

Some practitioners hope that 'one size will fit all' and use premixed insulins, which have basal and bolus insulins in fixed proportions (usually 70%:30%). In clothing, the size XL will fit all but will not do so very comfortably or elegantly. For patients with type 2 diabetes, premixed insulins rarely fit anyone and additionally cause several problems. The quick acting insulin can cause hypoglycaemia and extra weight gain, and the fixed proportions of the two types of insulin can make titration difficult because changing the dose changes both the basal and the bolus components.[4]

Eventually, many people with type 2 diabetes will require quick or very quick acting insulin to achieve the A_{1c} target of less than 7.0%.[5]

Stopping oral hypoglycaemic agents

Generally, oral hypoglycaemic agents should be continued unless there is a reason to stop them (such as renal impairment). Stopping oral hypoglycaemic agents is likely to worsen glycaemia because they were probably having some hypoglycaemic effect. For example, metformin and/or glitazones increase insulin sensitivity (and thereby reduce insulin resistance) and sulfonylureas and glitinides increase insulin secretion. Furthermore, stopping metformin removes its beneficial effects in terms of weight control (Table 1). Metformin as monotherapy for six months is associated with weight loss (about 2 to 3 kg)[6] as opposed to the weight gain associated with monotherapy with both sulfonylureas and glitazones (about 2 to 3 kg the wrong way),[7,8] a net weight advantage of 4 to 6 kg for metformin.

The insulin sensitiser metformin will continue to be useful for as long as it can be safely used and is tolerated because insulin resistance continues and/or worsens with time. However, the effect of insulin secretagogues such as the sulfonylureas progressively decreases as the capacity of the pancreas to secrete insulin decreases.

Not anticipating weight gain with improved glycaemic control

Hyperglycaemia is associated with glycosuria; the potential energy associated

with the glucose is also lost in the urine. Improving glycaemic control will reduce or stop glycosuria and is likely to produce weight gain because the previously excreted glucose now becomes available for metabolism. The greater the improvement in glycaemia, the more the decrease in glycosuria and the greater the weight gain. As a rough rule, 2 kg is gained for each 1% decrease in A_{1c} when insulin is started (Table 1).

Other factors may contribute to weight gain. For example, people may feel like eating more because they feel better when their hyperglycaemia is controlled, and overenthusiastic insulin therapy can produce hypoglycaemia with its associated desire and need for extra food intake.

When people with type 2 diabetes start insulin, they should be encouraged to 'eat less and walk more' to balance the expected effects of reduced glycosuria.[9]

Difficulty losing weight

You reintroduce the metformin and switch Sue from twice daily premix to bedtime basal insulin. You also suggest she get some dietetic advice. She returns 10 weeks later.

'Your medication change and the dietary advice seem to be working. Initially my weight went down rather than up. I lost 2 kg in the first six weeks. But now I'm stuck. My weight hasn't changed for the last few weeks.'

Why is Sue no longer losing weight?

Again consider potential complicating conditions and medications. However, the common causes for patients reaching a weight plateau are:

- eating extra carbohydrate to 'balance' the insulin
- patient and/or doctor aiming for 'tight' glycaemic control
- walking 'more' but not enough.

Extra carbohydrate to 'balance' the insulin

Some people on insulin are advised to eat extra complex low glycaemic index (GI) carbohydrate at meals, between meals, before bed and before exercise to 'balance' the hypoglycaemic effects of medication and exercise. The extra snacks are thought to 'spread' the glycaemic load more evenly throughout the day.

This advice may be well intentioned and theoretically sound but it may make it impossible for a person using insulin to control their weight. Asking people taking insulin to increase their carbohydrate intake and eat six times a day is asking them to put on weight.

Extra carbohydrate on its own would not necessarily cause a problem if it were balanced by a lesser intake of other major nutrients, particularly fat. Usually, however, people eat the extra carbohydrate as well as their normal meals. Moreover, they don't just eat extra carbohydrate, they eat extra other energy sources as well – for example, the extra slice of bread might come with butter, cheese, ham or mayonnaise, or all of these.

People with diabetes should adjust their hypoglycaemic medication to suit their lifestyle, rather than vice versa. If hypoglycaemia occurs, they should decrease hypoglycaemic medication rather than increase carbohydrate. If the person is worried about hypoglycaemia when exercising, then the solution is, once again, to decrease hypoglycaemic medication.

If the overnight or fasting BGL is low in a person taking basal bedtime insulin and daytime oral hypoglycaemic agents, decrease the insulin. If the low BGL occurs during the day, decrease the oral hypoglycaemic agents (particularly the sulfonylurea). If the person is on twice daily basal insulin, you will probably have already stopped the sulfonylurea. Hypoglycaemia during the night should prompt a decrease in the bedtime insulin dose, and hypoglycaemia in the day should prompt a decrease in the morning insulin dose.

Aiming for 'tight' glycaemic control

The glycaemic target of A_{1c} below 7% is based on data from the Diabetes Control and Complications Trial (DCCT) for type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) for type 2 diabetes.[7,10] As seen in Figure 1, the risk of microvascular complications (retinopathy) in type 2 diabetes increases

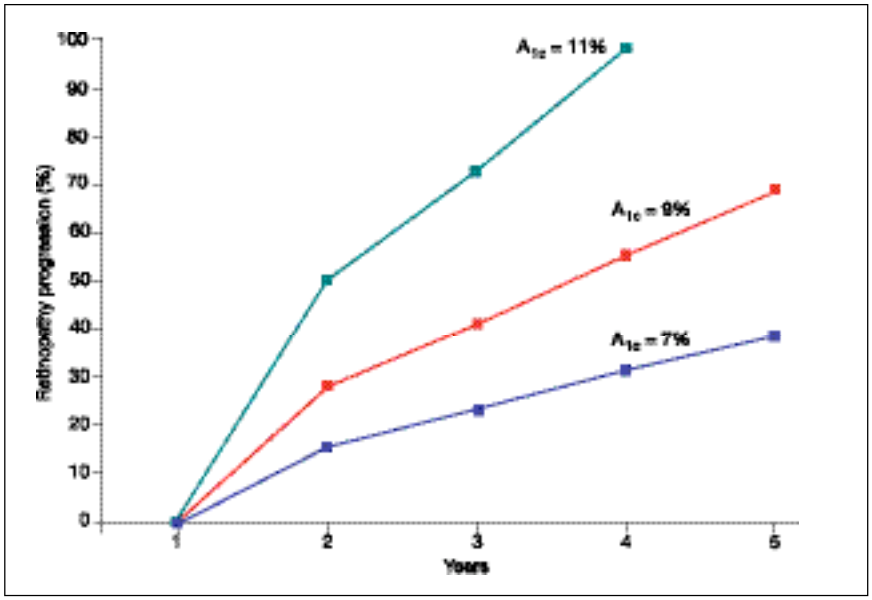


Figure 1. Retinopathy increases with time and with increasing A_{1c} levels. (Retinopathy progression defined as a two-step change in grade of the condition.)[7]

continued

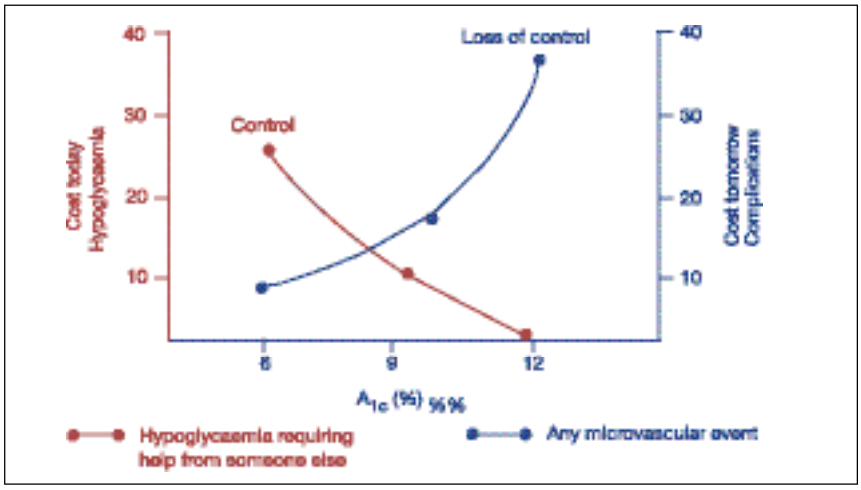


Figure 2. The person with diabetes is faced with a choice between the risk of diabetes complications with worsening control and the cost of extra self and medical care plus the risks of hypoglycaemia and weight gain.[7]

progressively with time, and more rapidly as the A_{1c} rises. Even at an A_{1c} of 7.0%, there is progression (35% progression of retinopathy over five years). This has led some people to propose lower A_{1c} targets (below 6.5%, for example)[11,12] and others to point out that the ideal target is normoglycaemia (that is, A_{1c} below 6.0%).

The 'price' to be paid for minimising the future risk of complications is weight gain, hypoglycaemia and patient effort and expense (Figure 2).[7] For each 1% decrease in A_{1c}, the progression of microvascular complications decreases by about 30%; however, the risk of hypoglycaemia increases by 25%, weight is gained (about 2 kg per 1% decrease in A_{1c}) and the patient (and doctor) have to work harder.

Obviously glycaemic targets must be individualised. While 'tight' glycaemic control may be an appropriate target for a young woman planning a pregnancy, less 'tight' control would seem more appropriate for an octogenarian with newly diagnosed diabetes who lives alone and whose memory is failing.

The current A_{1c} target of below 7.0% is the generally accepted compromise between the benefits and costs of improving glycaemic control.

Walking more but not enough

Objectively measuring physical activity can give people an unpleasant surprise. Many of us are busy all day and feel physically and mentally exhausted when we get home to relax in front of the TV with the remote control. If we were to wear a pedometer to measure our steps, we might find we had walked fewer than 3000 steps during the day. We would not be alone; half of Australian adults are not engaging in regular physical activity.[13]

Adding objectivity has two advantages:

- it can provide a baseline at the start of activities so realistic targets are set
- it provides feedback to monitor progress.

Activity can be measured in various ways, such as pedometers, time, number of blocks or meters on gym equipment.

Walking suits most people, and walking with a companion (human, canine or music) makes it enjoyable. People can add extra incidental activity into their day – for example, taking the first car parking space rather than cruising to find the closest one and taking the stairs rather than the lift.[9] The long term goal might be 30 to 40 minutes or 10,000 steps per day, and could be achieved in a series of steps from the baseline (e.g. 10% increments every one to two weeks). The message is to 'walk more, walk each day, and walk more each week'.

The general practitioner has a key role in prescribing, encouraging and monitoring activity for people like Sue who find it difficult to control their weight.

BGL and exercise

'I've done as you suggested and I'm up to 4000 steps a day. But my blood glucose goes up when I walk, not down. This morning I started at 6.2 and when I got back I was 8.3. I thought exercise was supposed to help me control my diabetes, not make it worse!'

Why does exercise make Sue's blood glucose go the wrong way?

Sue's raised BGL when she exercises may be caused by:

- blood glucose results not being totally reproducible
- her eating before she walks
- blood glucose initially increasing and then decreasing as activity continues.

Reproducibility of blood glucose results

Blood glucose meters are now smaller, faster, easier to use and more accurate, reliable and reproducible than ever before. But they are not perfect, nor people-proof.

Technique is important when using meters, and mistakes are easily made (Table 2). Some mistakes may be detected by watching the person do a test, others when the meter and strips are checked. Arrange for quality control tests (using a quality control fluid for the meter); this service may be available at some diabetes centres or branches of Diabetes Australia. Alternatively, ask Sue to perform blood glucose measurements immediately before and immediately after providing a blood sample for a laboratory glucose measurement – checking her results against the laboratory result will show the accuracy (how close her mean value is to the laboratory result) and reproducibility (how much

her blood glucose results differ) of her measurement.

Even with meticulous technique, BGL readings may be plus or minus up to 20% of the mean value; in Sue's case, 6.2 and 8.3 may be variations around a mean of 7.2 mmol/L. However, if Sue repeatedly measures her BGL as increasing then it is probably a real phenomenon.

Eating before walking

Blood glucose levels rise after meals regardless of whether people have diabetes but the increase is much more in those with the condition (for example, by up to 8 mmol/L compared with about 3 mmol/L). If Sue had eaten breakfast before her morning walk, her BGL would be expected to increase, the degree of increase depending on the glycaemic index and amount of carbohydrate she ate (the glycaemic load) as well as the other nutrients consumed (particularly fat).[14] The values of 6.2 and 8.3 mmol/L could simply be part of Sue's blood glucose profile after breakfast.

Sue may be wise to eat her usual breakfast before she walks, particularly if she plans to walk briskly and for a long time. She then won't have to worry about hypoglycaemia or to eat extra food, which would counteract the beneficial effect of the walking on her weight. The activity may also limit the blood glucose rise after breakfast.

Blood glucose may increase initially then decrease with activity

The blood glucose response to physical activity depends on the insulin levels, food intake and intensity and duration of exercise. In people without diabetes, activity triggers a sympathetic response (catecholamines) that increases hepatic glucose output to provide the muscles with glucose; insulin secretion in response to the increased blood glucose prevents any 'overswing' to hyperglycaemia. In people with diabetes, particularly type 1 diabetes, beta cells have partially or totally lost the capacity to control hepatic glucose output. If insulin levels are low, a sympathetic response triggers excessive hepatic glucose output, leading to hyperglycaemia. On the other hand, if insulin levels are high (from insulin secretagogue or injection), hepatic glucose output is reduced and blood glucose will fall, leading to hypoglycaemia.

As activity progresses in a person without diabetes, the tendency for blood glucose levels to fall is countered by decreasing insulin levels leading to lesser inhibition of hepatic glucose output and, therefore, a continuing glucose supply maintaining normoglycaemia.

In people with diabetes, this normal response to continued activity may be disturbed. In those receiving insulin or insulin secretagogues, the capacity to decrease insulin levels in response to falling blood glucose is reduced or absent, with the result that blood glucose progressively decreases with continuing activity as glucose is taken up by cells. People with diabetes who take insulin or insulin secretagogues are 'between a rock and a hard place': too little insulin, and blood glucose initially increases and may continue to increase; too much insulin, and blood glucose initially decreases and will continue to decrease.

Many people with type 2 diabetes have some residual beta cell function and the blood glucose response to activity is controlled to some degree. However, in type 1 diabetes and type 2 diabetes of long duration, the beta cell response is absent or inadequate and the blood glucose response to activity can be difficult to control.

Summarising the above, there is a biphasic response because:

- there is an initial increase in blood glucose as hepatic glucose output increases excessively because beta cells do not respond normally, and
- with continuing activity, blood glucose progressively falls because insulin levels do not fall (insulin continues to be absorbed from an injection site or secreted by the beta cell under the influence of a secretagogue).

Table 2. Blood glucose monitoring: tips and traps

Tips	Traps
Clean the sample site	Dirty meter
Use enough blood	Expired battery/strip
Maintain the meter	Incorrect strips, calibration or code
Check meter accuracy	Insufficient or smeared blood on strip

Travel

Sue is flying from Sydney to Los Angeles to visit Disneyland, Hollywood and the Universal Studios and then go on a bus tour to Las Vegas. She wants advice on how to handle her medication.

She is currently taking intermediate insulin (isophane) 35 units at breakfast and 16 units at bedtime and metformin 850 mg twice daily.

What should she do?

Adjusting insulin dosages

When travelling by air it may be necessary to adjust insulin dosages on the day of travel to allow more easy synchronisation of meal and injection times with 'local' time on arrival at a destination. Adjustment is advisable if the time zones of the departure and destination points differ by more than four hours (more than four time zones crossed).

If patients keep following the local time of the place of departure until their arrival at the destination (i.e. they don't change their wristwatch until the destination is reached), they can keep track of their insulin injections and meals. The time difference they will experience in changing to the local time on arrival at the destination

Useful resources for type 2 diabetes

- **Diabetes Australia.** Comprehensive series of consumer information resources including multilingual resources. www.diabetesaustralia.com.au/education_info/sheets.html and www.diabetesaustralia.com.au/multilingualdiabetes/HealthPros/index.htm
- **Diabetes Centre.** Professional and consumer resources. www.diabetes.org.au
- **National Diabetes Services Scheme.** Services available include subsidised blood glucose testing strips, free syringes and pen needles, and subsidised insulin pump consumables. Registration forms available from Diabetes Australia, phone 1300 136 588, or via the website, www.diabetesaustralia.com.au
- **RACGP.** *Diabetes Management in General Practice Guidelines 2006/7* available through regional divisions of general practice and at www.racgp.org.au

is the time difference between the place of departure and the destination, i.e. the number of time zones travelled across. The duration of the flight has no effect on the time difference because that time will pass whether the local time at the place of departure or the destination is followed.

The general rules for air travel are:

- if the day of travel is shorter – as it will be if travelling to a time zone 'ahead' of the local time, i.e. travelling east (in this case, Australia to USA) – then less insulin is needed
- if the day of travel is longer – as it will be if travelling to a time zone 'behind' the local time, i.e. travelling west (USA to Australia) – then more insulin is needed.

The changes in insulin doses are roughly proportional to the amount of time by which the day of travel is shorter or longer but, to be on the safe side, slightly lower (see Table 3).

It is not usually necessary to adjust for time zones when flying within Australia as time differences are less than four hours.

Travel across the Pacific Ocean involves crossing the International Date Line and patients may wonder if this will affect the adjusting of insulin dosages. It doesn't, because insulin dosages are considered over 24-hour periods so the 'gain' or 'loss' of a day involved crossing the Line becomes irrelevant.

The day Sue is travelling to California, which is six time zones to the east of Australia's eastern seaboard, her day will effectively be six hours shorter (although it will be 18 hours longer according to the calendar) – if she arrives at 6.00 a.m. in Los Angeles it will be midnight in eastern Australia. She will therefore need less insulin the morning before departure because this is the insulin that will be working during her travel.

Table 3 gives some examples of insulin adjustments. From this, it can be seen that the action required for travel east from Sydney to Los Angeles is a 20% decrease in insulin. So Sue should be advised to reduce her breakfast dose from 35 to 28 units on the day of travel, and to adjust the dose and time of her bedtime insulin to 80% of the usual dose (13 units, instead of

Table 3. Examples of insulin dosage adjustments for different time zones

Destination (from Sydney)	Destination time zone	Local destination time at noon Sydney time (+10 hours GMT)	Length of day of travel	Recommended insulin dosage change*
Honolulu	–10 hours GMT	4 pm	4 hours shorter†	No change necessary
London	GMT	2 am	10 hours longer‡	Increase neutral insulin by 10% before extra meals
New York	–5 hours GMT	9 pm	9 hours shorter†	Reduce insulin by 25% on day of departure
Los Angeles	–8 hours GMT	6 pm	6 hours shorter†	Reduce insulin by 20% on day of departure
Tokyo	+9 hours GMT	11 am	1 hour longer‡	Eat an extra 15 g of carbohydrate 1 hour before next insulin dose, destination local time
Wellington	+12 hours GMT	2 pm	2 hours shorter†	No change necessary

* Adapted from *Diabetes and You – the Essential Guide*, published by Diabetes Australia, 1999, revised 2002. † Flight eastwards, crossing the International Date Line. ‡ Flight westwards.

16) taken six hours earlier than she would normally (at, say, 4 p.m. Sydney time rather than 10 p.m. Sydney time).

When she arrives in California, Sue should adopt the local time for meals and medication. She should take her usual medication (insulin and metformin) when she has her breakfast on the morning of arrival (flights from Sydney to Los Angeles arrive in the early to mid-morning Los Angeles local time). Las Vegas is in the same time zone as Los Angeles so Sue will be able to keep to her new local time when she travels there by bus.

On her return journey to Australia, Sue's day will be six hours longer so she will need extra meals with short acting insulin (one-third of her usual morning basal insulin dose [35 units], i.e. 12 units) to cover the extra time. When she arrives home she should once again adopt local time for medication and meals.

The patient handout on pages 39 and 40 gives some guidelines on air travel for people taking insulin.

Other travel considerations

In addition to advice on adjusting her hypoglycaemic medications, there are some general tips you can give Sue to help her enjoy her long distance flight without hassles. These include:

- she should eat regular meals and snacks and make time for physical activity
- most agencies will make special arrangements for food for people with diabetes, but Sue should carry her survival kit, including extra food, just in case (see the patient handout on pages 39 and 40)
- she should take several copies of a letter from you stating that she has diabetes, takes insulin (and other medications), needs to do blood tests and may need special arrangements for food and activity (she should carry one copy of this in her hand luggage)
- she should carry a full set of diabetes supplies (blood glucose monitor and strips, insulin injectors and insulin) in her hand luggage and also pack extra insulin and, if possible, a spare set of the other equipment in her check-in luggage. It is advisable to check the particular airline's regulations regarding the carrying of diabetes supplies early in the planning of a trip.

Further information

Diabetes Australia has produced information sheets for patients on various aspects of living with diabetes, including travelling – see the box on page 18.

Conclusion

Problems can occur in people who are managing their type 2 diabetes with insulin and oral hypoglycaemic agents. However, many of these can be avoided. Improved glycaemic control comes with the risks of hypoglycaemia and weight gain, but these problems can be avoided if the patient and doctor are aware of the risks and know the appropriate countermeasures. Patients need to be aware of the need for adequate physical activity, appropriate food intake and meticulous blood glucose monitoring.

When travelling, people with diabetes should carry a diabetes survival kit containing a full set of their diabetes medication and monitoring equipment, a letter from their doctor stating they have diabetes, and some carbohydrate-rich food. Long distance air travel is likely to involve adjustment of insulin dosages if more than four time zones are crossed. MT

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MedicineToday PEER REVIEWED ARTICLE

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KISS: 'keep insulin safe and simple'

Part 3: troubleshooting insulin problems in type 2 diabetes

The variable blood glucose levels that may occur in patients who have type 2 diabetes and are taking insulin can have several causes, including injection and blood glucose monitoring techniques, physical activity and eating schedules, concurrent illness and insulin type and dosages.

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The number of adult Australians with type 2 diabetes has doubled in the last 20 years. Almost all these patients are managed by general practitioners, and many of them will require insulin treatment. The reasons for general practitioners to start insulin sooner rather than later are quite clear:

- the Diabetes Control and Complications Trial (DCCT; in type 1 diabetes) and the United Kingdom Prospective Diabetes Study (UKPDS; in type 2 diabetes) established A_{1c} as the 'gold standard' index of glycaemic control with a clear relation to long term

IN SUMMARY

- **Using the correct injection technique minimises variation in insulin absorption. Injection site problems include fat hypertrophy, bruising, pain, occasionally allergy and rarely fat atrophy.**
- **On sick days (everyday illness or infections), patients should continue with insulin and hypoglycaemic medication, with the possible exception of metformin. Blood glucose should be monitored more frequently than usual, hydration maintained and supplemental insulin or medication considered. Hospital admission may be necessary.**
- **Blood glucose swings can be caused by variability in physical activity, food (glycaemic load) and hypoglycaemic medication and/or by concurrent illness, or related to injection and blood glucose monitoring techniques. Swings can usually be smoothed out by education of patients in these areas.**
- **The three classic patterns of morning hyperglycaemia are 'insulin run out', 'the bounce' and 'poor control'.**
- **There is a risk of severe hypoglycaemia in patients with type 2 diabetes, particularly in those with low A_{1c} values or who are older and/or have had diabetes for many years.**
- **Regularly review hypoglycaemic and other medication, self-management techniques (lifestyle, medication and monitoring) and action plans for sick days, hypoglycaemic episodes and mistakes in medication dosing, particularly in patients in whom problems have occurred. These patients should have 24-hour access to advice.**

Figure 1. A lump caused by repeated insulin injections in the same site.

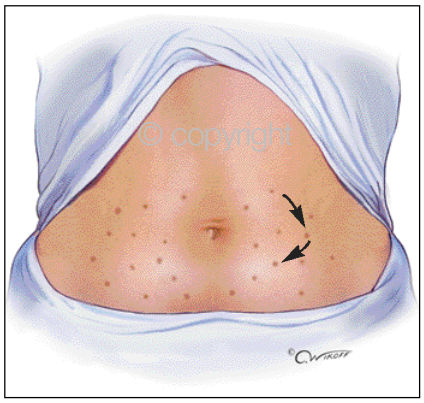

Figure 2. The preferred site for insulin injections is the abdomen. The site of the subcutaneous injections should be rotated, as shown by the spots.

microvascular diabetic complications[1,2]
- in Australia, national guidelines recommend measurement of A_{1c} in patients with type 2 diabetes at least annually[3]
- in Australia, evidence based recommended targets for A_{1c} are less than 7.0%[3]
- the UKPDS found that 50% of newly diagnosed people with type 2 diabetes required insulin therapy within six years to maintain A_{1c} below 7.0%;[4] this need for insulin occurs as the capacity of the pancreas to secrete insulin decreases
- 40% of Australians with type 2 diabetes have A_{1c} above 7.0%[5]
- the Western Australian Fremantle Diabetes Study showed that A_{1c} values in patients at the transition from using oral hypoglycaemic agents to insulin to control glycaemia were above A_{1c} values at the transition from lifestyle to oral hypoglycaemic agents (9.4 and 7.7%, respectively)[6]
- the evidence based recommended starting schedule for insulin in patients with type 2 diabetes is bedtime intermediate acting isophane insulin with continuation of oral hypoglycaemic agents[7]
- there are consensus recommendations for titrating insulin therapy for type 2 diabetes.[8]

Other articles in this series on insulin therapy using the KISS approach ('Keep Insulin Safe and Simple') give some guidelines to starting and living with insulin for patients with type 2 diabetes – see pages 5 to 19 (originally published in *Medicine Today*, March and April 2007).[9,10] This article reviews some problems that may occur with ongoing use of insulin and suggests ways to anticipate and avoid them, and to identify and manage them should they occur. The final article in the series uses a case study to illustrate the progression of insulin therapy and the titration of insulin in a patient with type 2 diabetes – see pages 28 to 34 (originally published in *Medicine Today*, June 2007).

Problems with the injection site

'The insulin is working OK but I'm getting these lumps where I inject. They are not uncomfortable but my wife is worried something might be wrong and when I wear my swimmers they look very obvious.'

John is 62 years old and has had type 2 diabetes for eight years. He started taking insulin eight months ago. His medications include intermediate acting isophane insulin (Humulin NPH, Protaphane) 36 units at bedtime, metformin 1 g twice daily and the sulfonylurea glimepiride (Amaryl, Aylide, Diapride, Dimirel) 4 mg/day.

- What are the lumps (see Figure 1)?
- What should John do about them?

The lumps

The formation of lumps is a common problem associated with repeated injections in the same site. The damage of repeated injections causes scarring, and the insulin, which is anabolic, causes fat hypertrophy. Patients may find these lumps unsightly but they also find them convenient to inject into and, because of nerve damage in the area, the injections may cause less discomfort. However, injecting into these lumps may be associated with variability of insulin absorption. One day, the injection may be into a scarred area, and the insulin may be slowly absorbed; another day, it may be into an unscarred area and absorbed normally.

John's response

John should ensure he is using the correct technique when he injects his insulin. Insulin should be given:

- subcutaneously, not intradermally or intramuscularly
- consistently in a given anatomical area, not in the abdomen one day and in the thigh the next (absorption is different in different anatomical areas)
- in sites that are rotated within the same anatomical area, so that local problems do not occur (Figure 2)
- without causing bruising, because this will affect absorption.

Checking injection technique and sites of injection is part of the annual review recommended by the RACGP for patients using insulin.[3] The abdomen is the preferred site for insulin injections. As well as insulin being less well absorbed when injected into other anatomical areas, it is difficult to use the correct technique when injecting into the arm and many people do not have sufficient subcutaneous fat on their thighs.

Injection site problems other than

lumps include:
- bruising
- pain
- allergy (occasionally)
- fat atrophy (rarely).

Sick day management

Helen, John's wife, is seeking your advice over the phone.

'John is sick with vomiting and diarrhoea. What shall I do about his insulin? He's nauseous and not eating but his blood glucose is 17.6.'

- What should Helen do about John's insulin?
- What are the signals that things are getting out of control?

Continue insulin

Everyday illness or infections will usually cause a rise in the blood glucose level (BGL) to outside the normal range in patients with diabetes. The key points in managing such patients are to:[11]

- ensure they continue taking their insulin and hypoglycaemic medication, with the possible exception of metformin (metformin may need to be stopped because it can worsen gastrointestinal problems or cause lactic acidosis if there is significant impairment of cardiovascular, renal or liver function)
- monitor BGLs more frequently than usual
- ensure adequate support for patients and their carers
- ensure the patients maintain hydration (and carbohydrate intake unless BGL exceeds 15 mmol/L)
- consider giving patients supplemental insulin or medication
- avoid hypoglycaemia in those with gastrointestinal disorders associated with nausea and vomiting
- consider hospital admission if their medical or metabolic condition worsens and/or they or their carers cannot cope.

Your advice to Helen about John's medication would be to continue his isophane insulin but to stop the metformin. As his BGL is high, he should take 4 units of quick acting insulin (10% of his total daily intermediate insulin dose) if he has access to it, and review his blood glucose in two hours. Either quick acting neutral insulin (Actrapid, Humulin R) or very quick acting analogue insulin (insulin aspart [NovoRapid], insulin lispro [Humalog]) may be used. If John's BGL is still high, he should repeat the short acting insulin supplement and, if the level continues to exceed 15 mmol/L, he should consider transfer to hospital. (The advice if the BGL exceeds 22 mmol/L is to take a dose of quick acting insulin equal to 20% of the total daily intermediate insulin dose, and follow the same procedure.)

It is important that Helen understands when John should be transferred to hospital. Apart from continuing hyperglycaemia, John is at risk of dehydration because of his vomiting and diarrhoea. If the vomiting prevented any fluid intake for more than four hours and/or there was continuing profuse diarrhoea, intravenous fluid and electrolyte therapy would be required. Helen should be encouraged to take John to hospital (or call an ambulance) sooner rather than later, and not feel obliged to cope on her own.

Fortunately, all went well – Helen coped and John recovered.

BGL variability

Six weeks later John reports another blood glucose problem.

'Up and down like a yoyo. Yesterday before lunch 5.6, beautiful. Today, sky high, 12 before lunch and "HI" after. I just can't get it right.'

- What might be causing the blood glucose variability?
- Should John change his insulin dose or type?

Sources of blood glucose variability

Blood glucose swings are usually caused by variabilities in physical activity, food (glycaemic load) and hypoglycaemic medication and/or by concurrent illness. These variabilities may be intended or unintended. John and Helen may not understand the effect of lifestyle change (activity and glycaemic load) on blood glucose, and John might make mistakes in his doses of insulin or tablets. A diabetes management update may be due. Occasionally the problem lies with the insulin itself. Out of date insulin or insulin that has been stored incorrectly (allowed to become too hot or too cold) may not retain its effectiveness.

Sometimes the cause of variable BGLs is less easily identified, and related to techniques used in giving injections and testing blood glucose.

Injecting insulin

As mentioned earlier, the technique used when injecting insulin can affect the absorption of the insulin. Alternatively, John may not be completely mixing the cloudy isophane insulin. Incomplete mixing of the protamine zinc insulin suspension (the 'cloud') means that variable amounts of insulin are given. Many patients do not realise the importance of thorough mixing in three dimensions and they just dial or draw up and shoot. Some mistakes can be picked up by watching the injection process from start to finish.

Table 1. Blood glucose monitoring: misleading information

Sources of misleading information include:

- Test results – dirty meter, expired or incorrect strips, incorrect calibration or codes, suboptimal patient technique
- Timing – lowest preprandial or highest postprandial BGL tested
- Recording – high or low values omitted, 'good' results made up

It should not be assumed that because a person has had diabetes for many years that his or her diabetes techniques are correct. Some people make the same mistakes over and over again. Patients may find helpful the handout entitled 'How to inject insulin' (see pages 35 to 38).

Blood glucose monitoring

The BGL results you are seeing may not be complete or correct. The current measuring systems are much simpler to use and give more accurate and reliable results than the older systems but blood glucose tests can still be done incorrectly (Table 1).[12] A quality control check and, as for injection, watching the process of testing from start to finish can identify problems.

The fasting (pre-breakfast) BGL is the most convenient for patients to check and often is the only one they do. Fasting values may give 'good' results as blood glucose often rises progressively through the day in patients with diabetes. The selective testing and reporting of fasting values may explain why the A_{1c} might predict a higher blood glucose than that reported. (Average BGL in mmol/L = $2A_{1c} - 6$. At an A_{1c} of 6%, the average BGL is 6 mmol/L; above this value, for each 1% A_{1c} increase, average BGL increases by 2 mmol/L). Patients should be asked to perform blood glucose tests before lunch and the evening meal as well.

In patients who have been told to check their BGL two hours after the evening meal (this is often the highest value for the day), the A_{1c} will predict a lower BGL than reported. Checking that the preprandial BGL and A_{1c} are both on target usually gives a reasonable picture of daily and long term glycaemia. If A_{1c} prediction and reported BGLs differ significantly then look for 'hidden' hyperglycaemic or hypoglycaemic episodes. Hypers 'hide' postprandially or during the night, and hypos 'hide' preprandially or during the night.

Doctors like to see and patients like to report 'good' results. Patients may omit high values because they think they are not representative or 'forget' to record them because they want 'good' numbers. Some patients have even been known to make up a week's results before the consultation. Checking the memory of the blood glucose meter may give you insight into the completeness and accuracy of a patient's records.

Patients who are reluctant to change their erratic physical activity or eating schedules, their misuse of alcohol or their nonadherence to medication do not often volunteer the cause of variable BGLs. Others may not remember events clearly enough to recognise something associated with higher or lower BGLs. If any of these factors are possible, a third party, like Helen, may be able to help.

Changing insulin

Usually blood glucose swings can be smoothed out by education in lifestyle, medication and diabetes techniques. If the person cannot reliably manage self-care routines and techniques because of incapacity or forgetfulness then a third party may need to take control of part of the diabetes management.

Changing the insulin dose or type may be necessary in some patients, for example:

- if the person cannot reliably mix the insulin, a clear long acting insulin analogue (detemir [Levemir]or glargine [Lantus]) would help solve the problem because it does not need mixing. Currently, glargine is subsidised by the PBS for all forms of insulin therapy in type 2 diabetes, and detemir is TGA-approved but not PBS-subsidised for use in type 2 diabetes.
- if the person has difficulty with the process of drawing or dialling up the insulin, or with the injection, the larger isophane insulin injecting device, InnoLet, might help. People with limited vision or manual dexterity find that the large clock face dial and the size of the device make it easier to see, dial up and inject.

John has had diabetes for eight years and may have nerve damage affecting the autonomic nervous system, which controls gastric emptying. Variable food delivery to the small intestine can cause unpredictable glucose swings. Usually there would be other signs of somatic or autonomic neuropathy, such as painful or painless peripheries and postural hypotension.

Morning hyperglycaemia

'My evening blood glucose was always high so I switched the insulin injection to the morning. Now my morning glucose is always high. Helen has cut back my eating starchy vegetables, bread and sweets at tea and I've even started walking before bedtime, but my blood glucose is still high. Should I cut out more carbohydrate or increase my insulin?'

John's fasting BGL of 7 to 10 mmol/L is high but the other values – lunch and tea, both 4 to 7 mmol/L, and bedtime 7 to 10 mmol/L – seem to be on target. He is now on 45 units of intermediate insulin in the morning.

- Should John eat less carbohydrate?
- Should he increase his insulin?

Carbohydrate cuts

John does not need to cut out more carbohydrate from his diet. People often believe that the food they eat in the evening affects the BGL the next day, such as 'the chocolate biscuit I ate at bedtime' being the reason for their high fasting glucose. However, this is not so, unless they eat a very large amount of carbohydrate late in the evening.

During the night, the glucose from the evening food is cleared from the circulation and the liver supplies glucose to the blood. The morning blood glucose reflects hepatic gluconeogenesis, not the effect of the previous evening meal or snack. Further carbohydrate cuts will not solve John's morning hyperglycaemia

but might make him hypoglycaemic when he goes for his walk before bedtime.

Insulin increase

John does not need to increase his morning insulin. In both people without and those with diabetes, blood glucose falls during the night and then increases in the early hours of the morning. The morning hyperglycaemia of this 'dawn phenomenon' can be a problem in people with diabetes. To sort out which of the three classic patterns of morning hyperglycaemia is occurring in John's case, ask him to check his BGL before bed, at 2 a.m. and upon waking in the morning. The three patterns – 'insulin run out', 'the bounce' and 'poor control' – are described in the box about morning hyperglycaemia on this page.

It is most likely that John's daily dose of basal insulin given in the morning is 'running out' by the next morning. Remember that as type 2 diabetes progresses, insulin secretion progressively decreases (and insulin resistance progressively increases). John's pancreas may have produced enough insulin to control night-time glycaemia a few years ago but may no longer have that capacity. A bedtime dose of basal insulin will control night-time glycaemia and can be titrated to keep fasting BGL on target. The morning dose will continue to control basal daytime glycaemia.

It should be noted that a similar situation can occur with a single basal bedtime insulin dose. The fasting glucose may be well controlled but the blood glucose rises before lunch and/or the evening meal. This is what happened to John before and prompted him to change his insulin schedule. Increasing the bedtime dose will cause night-time or morning hypoglycaemia but blood glucose through the day will remain high. In this case, a morning dose should be added to control daytime glycaemia and the bedtime dose continued to control night-time and fasting blood glucose.

Three classic patterns of morning hyperglycaemia

A: 'Insulin run out'

In 'insulin run out', the patient's blood glucose rises steadily through the night. This is a particular problem in people on single morning dose insulin schedules using human intermediate insulins as increasing the morning dose might cause hypoglycaemia through the day. An evening injection might be necessary.

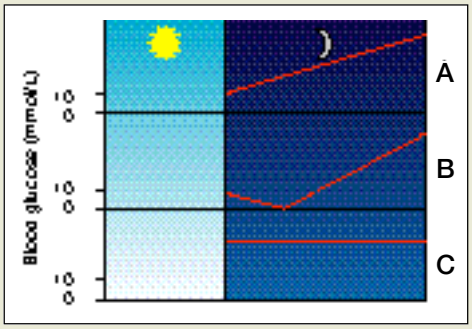

Figure. Morning hyperglycaemia: three patterns.

B: 'The bounce'

In 'the bounce', the patient's blood glucose falls to hypoglycaemic levels and then increases. This is the classic 'Somogyi effect' in which hypoglycaemia during the night causes physiological responses that lead to morning hyperglycaemia. Checking the 2 a.m. BGL will identify 'the bounce'. Although this pattern is uncommon, when it does occur less insulin is required.

C: 'Poor control'

In this situation, the patient's blood glucose is high before bedtime and high through the night. The morning hyperglycaemia reflects general hyperglycaemia. The insulin dose will need to be adjusted to achieve better control in the evening as well as through the night.

Risk of severe hypoglycaemia

John doesn't like the idea of taking insulin at bedtime.

'I could have a bad hypo. If I'm asleep, I won't know if my blood glucose is going low.'

- How likely is severe hypoglycaemia?
- What factors make severe hypoglycaemia more likely?

Likelihood of severe hypoglycaemia

Patients with severe hypoglycaemia need help from another person to prevent or treat loss of consciousness.

Many people think all those using insulin are in the same category. When a person with 'non-insulin dependent' (type 2) diabetes needs insulin, they think the diabetes has become 'insulin dependent' and that the person is then prone to the wide glycaemic swings and hypoglycaemic risk associated with type 1 diabetes. However, the pathophysiology of the two types is very different, as is the likelihood of glycaemic swings.

In patients with type 1 diabetes, practically no endogenous insulin is produced. If the insulin dose is exactly right, blood glucose is on target. More insulin requires the body to 'counter-regulate'. The sympathetic nervous system and hypothalamic pituitary adrenal axis are activated and glucagon is secreted, as long as these responses have not been affected by autonomic neuropathy (sympathetic nervous system) or by abnormal alpha cell regulation (glucagon), both of which can occur in those with type 1 diabetes. This overall response is associated with symptoms. If the insulin excess is considerable, counter-regulation may be overcome, blood glucose progressively falls and the person loses consciousness.

In patients with type 2 diabetes, endogenous secretion continues and endogenous insulin levels may be even higher than in people without diabetes because

continued

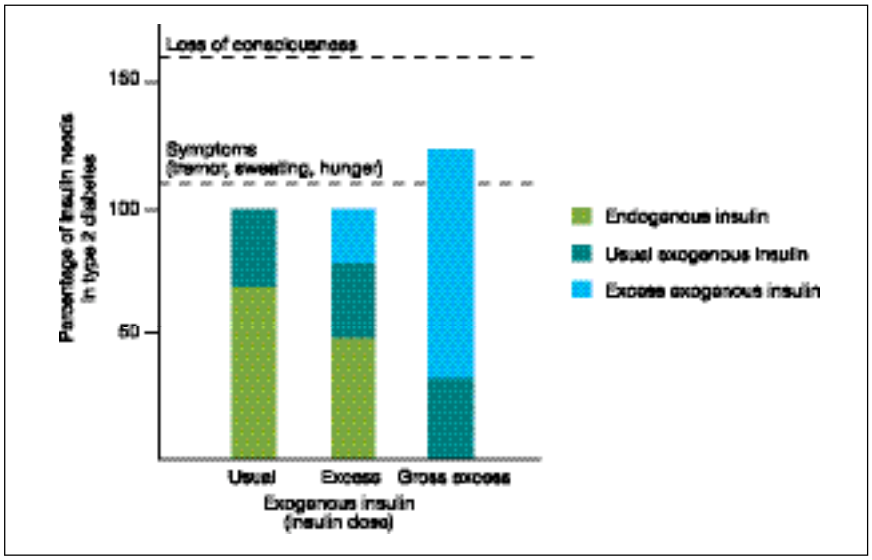

Figure 3. Insulin dose and hypoglycaemia. In patients with type 2 diabetes, endogenous insulin secretion decreases if excess exogenous insulin is taken (centre bar), reducing the risk of severe hypoglycaemia. Endogenous insulin can be totally supressed if a gross excess of exogenous insulin is taken (bar on right). (Derived from data in references 1 and 2.)

high insulin levels are required to overcome insulin resistance. Exogenous insulin supplements the endogenous insulin but is only part of the total circulating insulin (Figure 3). If excess insulin is taken, blood glucose falls a little, endogenous insulin secretion decreases and the balance between insulin and glycaemia is restored. Even if a large excess is taken, the potential for suppression of endogenous insulin secretion reduces the risk of severe hypoglycaemia (Figure 3).

This expected lower rate of hypoglycaemia in patients with type 2 compared with type 1 diabetes was shown in the two trials assessing the relation between glycaemia and complications, DDCT and UKPDS.[1,2] At the same level of glycaemia (A_{1c}), the risk of severe hypoglycaemia in patients with type 1 diabetes was very much higher than in those with type 2 diabetes.

There is, however, still a risk of severe hypoglycaemia in patients with type 2 diabetes, particularly in those who have low A_{1c} values or who are older, have autonomic neuropathy or have had diabetes for many years (in whom endogenous insulin secretion is low and whose diabetes resembles type 1).

Factors increasing hypoglycaemic risk

Personal, medical, medication related and diabetes management factors increase the risk of hypoglycaemia (Table 2). These factors increase the hypoglycaemic effect of insulin, reduce the effectiveness of counter-regulation or delay recognition of hypoglycaemia.

Type 2 diabetes is much more common in older people and, because of their age, these people are more likely to have social and medical problems and to be taking potentially dangerous medications. As people with diabetes age they develop all these problems as well as microvascular complications (loss of vision, renal impairment and somatic and autonomic nerve damage). Moreover, as noted above, the risk of severe hypoglycaemia increases as diabetes progresses.

This increased risk of severe hypoglycaemia with age may also be associated with an increased likelihood of permanent neurological damage if hypoglycaemia occurs. A 'watershed' area in the brain, with marginal blood and oxygen supply, is susceptible to hypoxic damage associated with decreased blood supply (e.g. as with hypotension). The marginal circulation also delivers a marginal glucose supply, and decreases in blood glucose can cause the same permanent damage as hypoxia.

Hypoglycaemia is more likely in older people because they are more likely to have hypoglycaemic risk factors. Hypoglycaemia in these patients is more likely to have catastrophic effects, including myocardial infarct, stroke, seizure or trauma caused by falling.

An often underestimated risk for hypoglycaemia is living or sleeping alone. John has Helen to notice disturbed sleep, night-time sweating or morning unconsciousness. She can also help with recovery or can phone an ambulance.

In patients with a history of severe hypoglycaemia and in those with hypoglycaemic risk factors, the following should be reviewed:

- hypoglycaemic and other medication (e.g. by a Home Medicines Review)
- self-management techniques (lifestyle, medication and monitoring)
- action plans for sick days, hypoglycaemic episodes and mistakes in medication dosing, and 24-hour access to advice.

Conclusion

Keeping insulin safe and simple (the KISS approach) in patients who have type 2 diabetes and are taking insulin requires anticipation and avoidance of problems, and management of them if they occur (Table 3).

Blood glucose swings can be caused by variability in physical activity, food and hypoglycaemic medication and/or by concurrent illness. However, it may be that the blood glucose results being reported by patients are not complete or correct because of inaccurate monitoring

Table 2. Type 2 diabetes: hypoglycaemic risk factors

Personal
- Erratic lifestyle
- Lives/sleeps alone
- Older age
- Longer diabetes duration

Medical
- Liver and/or renal dysfunction
- Hypothyroidism and/or adrenalism
- Autonomic neuropathy

Medication
- Affecting sulfonylurea pharmacokinetics:
  - sulfonamides
  - cimetidine
  - azole antifungal agents
  - NSAIDs
  - fluoxetine
  - fluvoxamine
- Causing hypoglycaemia or reducing response:
  - alcohol
  - beta blockers
  - ACE inhibitors
  - high dose salicylates
  - perhexiline

Management
- Lifestyle
- Medication adherence
- Diabetes techniques (injection, monitoring)

technique or selective testing and reporting. The patient's injection technique, including site of injection and mixing of cloudy insulin, should also be checked to ensure that day-to-day insulin absorption rates are relatively constant. Blood glucose swings can usually be smoothed out by education in lifestyle, medication and diabetes techniques. Changing the insulin type is not usually necessary.

When a person cannot reliably manage self-care routines and techniques because of incapacity or forgetfulness then it may be necessary to simplify the insulin schedule and/or for a third party to take control of part of the diabetes management.

A second dose of basal insulin (intermediate or long acting) may be required when the BGL is consistently above target 24 hours after a single daily basal insulin dose.

Action plans for sick days, hypoglycaemic episodes and mistakes in medication dosing should be in place, particularly for patients with a history of these problems. MT

Table 3. Type 2 diabetes and insulin therapy: getting and keeping blood glucose on target

- Check the blood glucose level (BGL) readings are accurate
- Check the patient's adherence to lifestyle recommendations and medications
- Check the injection technique and expiry date and storage of the insulin
- Regularly review the insulin type and schedule
- Remember the potential overnight variability of BGL and assess the patient's overall diabetes management if fasting BGL is not controlled
- Prevent hypoglycaemia
- Provide action plans for sick days, low BGLs and mistakes in medication dosing

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KISS: 'keep insulin safe and simple'

Part 4: titrating insulin in type 2 diabetes

A case study is used to illustrate the typical progression of insulin therapy in patients with type 2 diabetes and the titrating of insulin to keep blood glucose levels and A_{1c} on target.

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The United Kingdom Prospective Diabetes Study (UKPDS) showed that to keep type 2 diabetes under control (A_{1c} below 7%), insulin was needed within six years for approximately 50% of patients (Figure).[1] Although starting insulin in patients with type 2 diabetes is safe and simple, the size and number of insulin doses can be expected to increase with time as insulin resistance increases and the capacity of the pancreas to secrete insulin decreases. Beta cell function is about 50% of normal at diagnosis of type 2 diabetes, and progressively decreases by 3 to 4% per year thereafter.[2] Eventually insulin therapy should be expected rather than considered extreme.

The first article in this series discussed the principles of initiating insulin therapy using the KISS approach – 'Keep Insulin Safe and Simple' (see page 5 to 12, originally published in *Medicine Today*, March 2007). The two subsequent articles discussed problems associated with insulin therapy (see pages 13 to 27, originally published in *Medicine Today*, April and May 2007).[3-5] This article uses a case study approach to discuss the typical progression of insulin therapy in patients with type 2 diabetes, and offers advice on titrating insulin to keep blood glucose levels (BGLs) and A_{1c} on target.

Initiating insulin therapy

Case scenario

Mary, aged 61 years, has had type 2 diabetes for eight years. She is now taking the maximum oral hypoglycaemic agents: metformin 1 g three times daily, glimepiride 4 mg in the morning and rosiglitazone 8 mg in the morning. Her weight is 78.5 kg and her height, 1.64 m; her BMI of 29.2 kg/m^2 indicates she is overweight but not obese. Her

IN SUMMARY

- **About 50% of patients with type 2 diabetes will require insulin within six years of diagnosis.**
- **Most people with type 2 diabetes begin insulin therapy with one daily dose of basal insulin and continue taking oral hypoglycaemic agents. As the diabetes progresses, it becomes necessary to introduce a second daily dose of basal insulin, and then doses of bolus insulin at mealtimes.**
- **A somewhat simplified protocol for insulin therapy is to:**
  - **first fix the fasting blood glucose level (BGL) – is bedtime basal insulin needed?**
  - **then tackle the evening BGL – is breakfast basal insulin needed?**
  - **treat any high postprandial BGLs – is a breakfast, lunchtime or teatime bolus insulin needed?**
  - **and check the A_{1c} – is the A_{1c} on target, or are there hidden hyperglycaemic episodes in the late morning, in the evening or at night?**

pre-breakfast and pre-evening meal BGLs are both between 6 and 9 mmol/L, and her A_{1c} is 8.0%.

There seem to be no apparent opportunities to improve Mary's glycaemia by lifestyle or medication change, or by treating a complicating medical condition. Starting insulin therapy seems to be the next step.

What basal insulin schedule do you recommend?

Basal insulin – either intermediate acting or long acting – may be given in the morning (before breakfast), at bedtime or at both these times to achieve target BGLs (4 to 6 mmol/L) and target A_{1c} values (below 7%). (The A_{1c} value reflects the overall average BGL, 24 hours per day over several weeks. Within the ideal ranges for A_{1c} and BGL, the 'numbers' approximate each other – i.e. at an A_{1c} of 6%, the average BGL is 6 mmol/L. However, at higher than ideal levels, the A_{1c} value is lower than the average BGL, a 1% A_{1c} increase corresponding to about a 2 mmol/L increase in average BGL.)[5]

As noted in the first article in this series, most people with type 2 diabetes who require insulin have one BGL that is the main problem (usually the fasting BGL but occasionally the evening prepran-dial BGL).[3] In these patients, it is likely that only one basal insulin dose is needed (usually a bedtime dose to control fasting BGL but occasionally a morning dose to control evening BGL).

From Mary's BGLs, it can be seen that she has both fasting and pre-evening meal hyperglycaemia. She has two options for starting insulin.

- Start with a bedtime dose of basal insulin. If fasting BGL is on target but the evening BGL is still high, a second morning basal dose can be added. This principle can be summarised as: 'First fix the fasting; then tackle tea.'
- Go straight to a twice daily basal insulin schedule, and then titrate the bedtime dose to control fasting BGL and the morning dose to control evening BGL.

The twice daily schedule has the potential to get both fasting and evening BGL on target more quickly. However, Mary may prefer a single shot and you may prefer to do one thing at a time (i.e. fix the fasting first and then, if necessary, the evening). In general, changing one item at a time makes it easier to identify the cause of any problems that might arise.

PHOTOLIBRARY

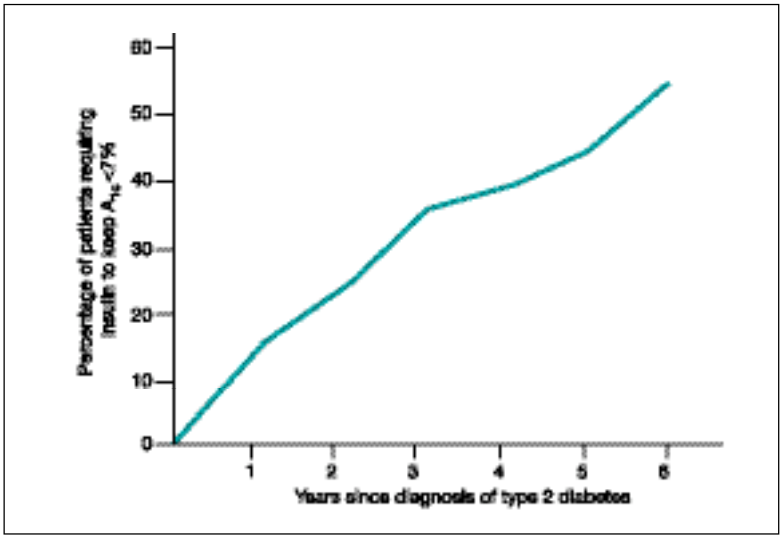


Figure. About 50% of patients with type 2 diabetes will require insulin within six years of diagnosis.[1]

The general recommendation is to start with 10 units of basal insulin at bedtime and increase according to the target BGL while continuing the oral hypoglycaemic agents at least until glycaemia is better controlled.[6,7] An example of an insulin titration protocol is given in the first article in this series.[3] The principles of insulin titration are:[8]

- when blood glucose is well above target, increase insulin doses by larger amounts than when blood glucose is close to target

- adjust doses every two to three days; even better, encourage the patient to change the dose following an agreed protocol, perhaps with advice from the practice nurse.

Occasionally, a single morning dose is appropriate when the fasting BGL is on target but the evening preprandial BGL is high. If the fasting and evening preprandial BGLs and the A_{1c} value are very high (e.g. A_{1c} above 10%), some practitioners recommend a twice daily dose of intermediate acting isophane insulin or a single daily dose of long acting analogue insulin as this provides the 24-hour insulin boost that is probably needed.

Intermediate acting isophane insulin (Humulin NPH, Protaphane) and the long acting analogue insulins glargine (Lantus) and detemir (Levemir) each have their pros and cons. The choice of which to use is often decided by the patient's choice of injection device – syringe, pen injector or, for those with limited vision or manual dexterity, the larger InnoLet (Table 1).[3] Analogue basal insulins have the advantages over isophane insulin of a more consistent profile, single rather than twice daily dosing and less risk of hypoglycaemia and not requiring mixing or resuspension before injection. There is, however, a slower response to dose changes with analogue basal insulin than with isophane insulin, and basal analogues may be confused with bolus insulins as both are clear solutions. Also, the analogue basal and bolus insulins cannot be mixed with bolus insulins, a flat insulin profile may not suit all patients, and glargine may sting when injected. Currently, glargine is subsidised by the PBS for all forms of insulin therapy in type 2 diabetes, and detemir is TGA-approved but not PBS-subsidised for use in type 2 diabetes.

Larger insulin doses and multiple oral hypoglycaemics

Case scenario

Six months later, Mary's blood glucose and A_{1c} levels are on target (fasting BGL mostly 4 to 6 mmol/L and an A_{1c} of 6.8%). Her hypoglycaemic medication includes three oral hypoglycaemic agents and 54 units of basal insulin at bedtime.

Table 1. Basal insulins

Insulin type	Trade name	Delivery device types
Intermediate acting		
Isophane	Humulin NPH	Syringe Reusable insulin pen
	Protaphane	Syringe Reusable insulin pen Disposable insulin pen A large disposable injection device (InnoLet)
Long acting – the analogue basal insulins		
Detemir	Levemir	Reusable insulin pen Disposable insulin pen
Glargine	Lantus	Syringe Reusable insulin pen Disposable insulin pen

Mary is concerned about 'all the insulin and tablets I am taking'.

How would you respond?

Insulin dose

In many people with type 2 diabetes there are two psychological barriers to optimising insulin therapy:

- starting insulin
- the large insulin doses required.

Patients (and often their doctors) may be reluctant to increase the insulin dose, particularly when the capacity of the injection device is exceeded or when the 'magic number' of 100 units per dose or per day is reached.

The average insulin dose to control glycaemia initially varies widely between patients,[9] and is affected by:

- glycaemic control – the higher the A_{1c} then the more insulin is required to control it
- insulin capacity – the longer the duration of diabetes, the lower the beta cell function
- insulin resistance – the more overweight and less active the person, the higher the insulin resistance.

The usual insulin dose required to control glycaemia is 40 to 80 units a day, but this can be expected to increase with time as beta cell function declines and/or insulin resistance increases.

Insulin has a number of biological effects that could theoretically be a problem (for example, its growth factor activity). However, apart from local effects at the injection site (fat hypertrophy), the associated weight gain (about 2 kg per 1% decrease in A_{1c}) and fluid retention, none have caused clinical problems.[4] On the positive side, the benefits in terms of glycaemic control were conclusively demonstrated in the UKPDS, where microvascular complication progression decreased by about 30% per 1% decrease in A_{1c} value.[4,10]

The practical implications of larger insulin doses include:

- a longer duration of the effect of

injected insulin as the volume (dose) increases more than the surface area for absorption in the subcutaneous insulin depot
- an injection device with a larger capacity may be more convenient
- splitting the insulin dose may be indicated, e.g. when the capacity of the injection device is exceeded.

Oral hypoglycaemic agents

Metformin has three advantages in patients with type 2 diabetes:
- insulin sensitising effects, which are beneficial for the duration of type 2 diabetes
- associated with weight loss, rather than with weight gain as with sulfonylureas, glitazones and insulin[10,11]
- demonstrated decrease in coronary events.[12]

Metformin is usually continued unless side effects occur (these are generally gastrointestinal) or it is contraindicated by the presence of renal impairment or the risk of hypoxic episodes that might cause lactic acidosis.

For Mary, reducing the number of times metformin is taken (for example, from three times daily to twice daily) and the total dose taken may be indicated because her renal function is likely to be impaired. Although estimated glomerular filtration rate (eGFR), the index of renal function, is now reported by laboratories with the creatinine value, the actual GFR should be calculated because metformin dosage adjustment is based on this rather than eGFR. Actual GFR can be calculated from the patient's plasma creatinine level using medical software or the Cockcroft–Gault formula.

The sulfonylurea glimepiride (Amaryl, Aylide, Diapride, Dimirel) is an insulin secretagogue and its hypoglycaemic effect would be expected to decrease with time as the capacity of the pancreas to respond declines. Stopping glimepiride would simplify the medication schedule, and it could be restarted if large increases in insulin dose were required to control glycaemia. Stopping the sulfonylurea may be premature now but may be appropriate later when a second basal insulin dose or a dose of bolus insulin is required.

Rosiglitazone (Avandia), like metformin, increases insulin sensitivity and would be expected to remain effective for the duration of type 2 diabetes. However, both glitazones and insulin can cause fluid retention, and stopping the glitazone may be necessary if peripheral or pulmonary oedema occurs.

Switching from isophane insulin to analogue basal insulin

When switching from isophane insulin to analogue basal insulin, consider the following:
- If changing from twice daily isophane insulin to once daily (single dose) analogue basal insulin, start at 80% of the total daily dose.
- If changing from once daily isophane insulin to once daily analogue basal insulin, use the same dose.
- If a premix insulin is used, calculate the new dose on the amount of isophane in the mix, e.g. 100 units of 30:70 premix has 70 units of isophane insulin (70%).
- Increase attention to eating, activity and monitoring schedules when changing insulins.
- Consider a 10% dose decrease (in addition to checking eating, activity and monitoring schedules) if severe hypoglycaemia has occurred in the past.

Morning but not evening BGL on target

Case scenario

Two years later, Mary's A_{1c} is 7.8% and her hypoglycaemic schedule includes metformin 500 mg twice daily and 96 units of basal insulin at bedtime. Her blood glucose profile shows:
- breakfast, 4 to 7 mmol/L
- lunch, 7 to 11 mmol/L
- evening meal, 6 to 9 mmol/L.

Table 2. Bolus insulins

Insulin type	Trade name	Delivery device types
Rapid acting (also known as very quick acting) – the analogue bolus insulins		
Insulin aspart	NovoRapid	Syringe Reusable insulin pen Disposable insulin pen
Insulin lispro	Humalog	Syringe Reusable insulin pen
Insulin glulisine	Apidra	Disposable insulin pen
Short acting (also known as quick acting)		
Neutral insulin	Actrapid	Syringe Reusable insulin pen
	Humulin R	Syringe Reusable insulin pen

How would you optimise glycaemic control?

The options for improving Mary's glycaemic control are to:

- increase bedtime basal insulin
- add a morning basal insulin dose
- add a morning bolus insulin dose.

Mary's BGL before breakfast is under control but that before the evening meal is not. It is now time to 'tackle tea'.

Titrating insulin is like tuning an old analogue radio – first get the coarse timing right with basal insulin, then fine tune with bolus if necessary. In Mary's case, considering her basal insulin:

- if her basal insulin is isophane (which has the relatively short duration of action of 12 to 24 hours), either add a second dose of isophane insulin before breakfast or switch to the basal analogue insulin glargine
- if her basal insulin is an analogue, add a second dose before breakfast.

Once again the choice of dose and the titration schedule are simple. Start with 10 units and increase according to the target blood glucose.

One potential problem might be that the morning dose necessary to control evening glycaemia (before the evening meal) produces lower values earlier in the day. This is not likely in Mary's case as her BGL before lunch was the highest value for the day. However, if it did occur, the response would depend on the type of basal insulin being used.

Isophane insulin has a peak of activity that might occur between breakfast and lunch, depending on the times of the meals. Such a peak might cause low blood glucose values before lunch and, as insulin levels decline after the peak, blood glucose might rise before the evening meal. The simplest solution would be to use an analogue basal insulin, which has a flatter profile than intermediate acting insulin, on either a twice daily or once daily schedule as this might provide sufficient basal insulin to control both fasting and evening glycaemia. Points to consider when switching from isophane insulin to analogue basal insulin are discussed in the box on page 31.

If the patient is already on analogue basal insulin or switching to one is considered too difficult (for example, because the insulin dose and/or injection device need to be changed), either a lifestyle or an insulin change is indicated:

- lifestyle change – bringing lunch closer to breakfast would provide more glucose earlier in the day and less later on, which might fix the problem of early hypoglycaemia and late hyperglycaemia
- insulin change – adding a dose of bolus insulin at lunch would provide more insulin to cover blood glucose up to the evening meal.

High pre-lunch BGL

Case scenario

Mary started taking a second dose of basal insulin in the morning. Initially blood glucose and A_{1c} were controlled. Eighteen months later, her A_{1c} is 7.5% and the problem BGL is before lunch, when values are consistently over 6 mmol/L.

How would you control lunchtime hyperglycaemia?

The following options could be considered to control hyperglycaemia at lunchtime:

- add a dose of bolus insulin before lunch
- increase the morning basal insulin dose
- add a dose of bolus insulin before breakfast.

Lunch bolus insulin

Adding a dose of bolus insulin before lunch would certainly 'fix' the high BGL at the time but the next day the BGL before lunch will be high again. Using bolus insulin after a high BGL has occurred does not address the problem. The hyperglycaemia needs to be prevented – that is, more insulin is needed before the high BGL occurs.

Morning basal insulin

Basal insulin controls the 'basal' BGLs before breakfast and the evening meal. As noted earlier, the morning basal insulin dose also affects lunchtime glycaemia. In the same way, the basal bedtime insulin dose can also cause hypoglycaemia during the night (fortunately much less often in patients with type 2 than in those with type 1 diabetes). Increasing the morning basal insulin dose will increase insulin levels before lunch, but because evening blood glucose is already on target the increase is also likely to cause evening hypoglycaemia.

Morning bolus insulin

A morning dose of a bolus insulin will increase insulin levels between breakfast and lunch, and bring the lunchtime BGL under control. However, it will have little effect after lunch. If the morning bolus insulin dose does result in a low BGL before the evening meal, the morning basal insulin dose could be decreased.

Titrating insulin

Although it is a simplification, titrate the basal insulins to control blood glucose before breakfast and the evening meal, and bolus insulins to control lunch and, occasionally, bedtime blood glucose.

Neutral insulin (Actrapid, Humulin R) and analogue bolus insulins (insulin aspart [NovoRapid], insulin lispro [Humalog], insulin glulisine [Apidra]) are subsidised by the PBS and each type has its pros and cons.[3] Analogue bolus insulins have the advantages over neutral insulin of being injected at the time of eating rather than a short time before, less risk of hypoglycaemia before the next meal and better postprandial glycaemic control. There is, however, the need for prompt intake of food after injection and for there to be carbohydrate in the meal, and there is the possibility of the insulin 'running out' before the next meal.

As for basal insulins, the choice of bolus

insulin is often guided by the injection device (Table 2). Alternatively, you may decide to stick to the same brand as the basal insulin. The safe and simple starting schedule is:

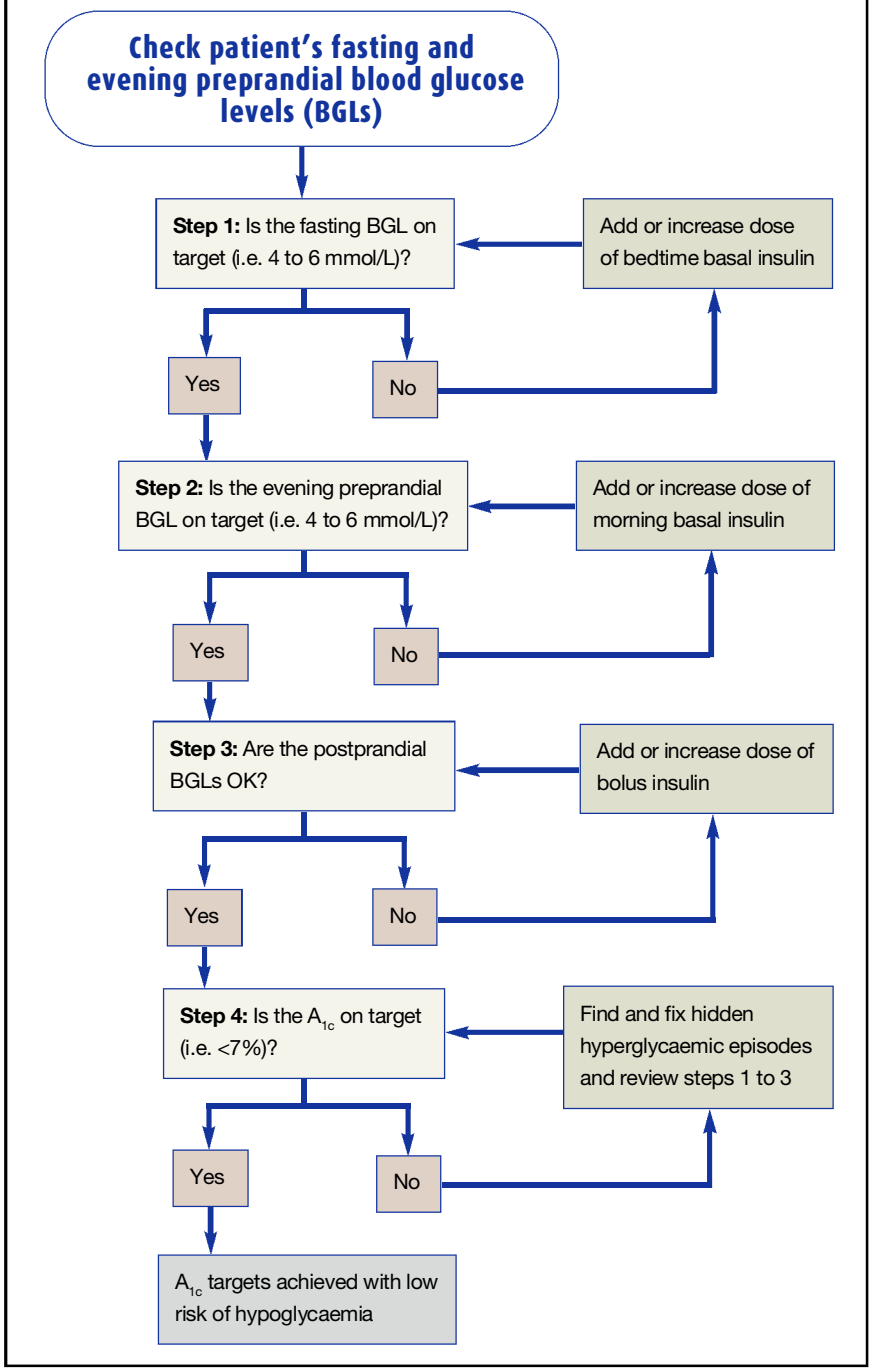
- start with 10% of the total daily basal insulin dose
- increase or decrease the dose by 20% when the BGL is well off target, and by 10% when values are closer.

If the BGLs before breakfast and tea have been under control (between 4 and 6 mmol/L), the A_{1c} value six to 12 weeks later should be close to target. If not, the task is to find and fix the 'hidden hypers'. These are usually in the first half of the day (late morning before lunch), at the end of the day (after a large evening meal that is followed by television watching and a few snacks) or during the night.

Sometimes patients will measure their BGL but not record the value and/or stop the measuring at that time so they will have 'good' numbers in their blood glucose record. Occasionally a patient may make up some or all of the BGL results. Patients do not need to check their BGLs four times during the day and in the middle of the night. If they can check their BGL once a day but at different times each day, they and you will get a good picture of their daytime blood glucose profile, even if they only do this several times a week.

If the record book is perfect and the A_{1c} value is above target, check the blood glucose meter's memory – you may find values that have not been recorded or recorded values that are not in the memory. Although the meters get better every year, they are not perfect or people-proof. Sometimes a check of the meter, blood glucose strips and patient technique is needed.[13] If the records and results are correct, hyperglycaemia occasionally 'hides' during the night (like hypoglycaemia). Blood glucose tests in the middle of the night will identify any night-time blood glucose problems.

An approach to titrating insulin



Conclusion

Most people with type 2 diabetes begin insulin therapy with one daily dose of basal insulin, usually at bedtime to control fasting BGL, and continue taking oral hypoglycaemic agents. As the diabetes progresses it is likely that evening hyperglycaemia will become a problem,

Troubleshooting insulin problems: a summary

'First fix the fasting
Then tackle tea
Find the hidden hypers
And check the A_{1c}'

- First fix the fasting – is bedtime basal insulin needed?
- Then tackle tea – is breakfast basal insulin needed?
- Find the hidden hypers – is a breakfast, lunchtime or teatime bolus needed?
- And check the A_{1c} – is the A_{1c} on target?

necessitating the introduction of a morning dose of basal insulin. Bolus insulins may then be required to control any postprandial hyperglycaemic episodes.

If the breakfast and evening BGLs are on target, the A_{1c} should be close to target. If it is higher then there are likely to be hidden hyperglycaemic episodes in the late morning, in the evening or at night increasing the average BGL and hence the A_{1c}. Sometimes, in an attempt to have a 'good' BGL record, patients do not record their BGL results as accurately as they might. Also, blood glucose testing equipment and patient technique needs checking occasionally.

The titration of insulin is summarised in the flowchart on page 33 and box on this page. MT

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How to inject insulin

Prepared by Dr Pat Phillips, Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

This handout provides a guide to the procedure of injecting insulin.

What is insulin?

Insulin is a hormone that helps keep blood glucose at normal levels (usually 3 to 8 mmol/L in people who do not have diabetes). People with diabetes often do not have enough insulin or it does not work very well. Injecting insulin replaces or tops up what your body would normally produce.

If insulin is taken by mouth, it is destroyed in the gut. It needs to be given by injection, usually in the fatty layer of the abdomen but sometimes in other areas of the body.

Types of insulin and timing of injections

Your doctor or diabetes educator will discuss with you the most appropriate type of insulin for your diabetes. The available insulins are listed in the Table below.

Equipment

There are many syringes, pens and other devices that can make injecting insulin easier:

- syringes – available in different sizes depending on your needs
- pens and similar devices – can be disposable or reusable (insulin is available in a cartridge that can be changed).

The fine needles used with the syringes and pens are also available in different sizes.

Ask to see the range of equipment so you can choose the injection device that best suits you.

If you use an insulin pen or a similar device, you should also know how to use a syringe in case your injector is lost or not working.

COPY FOR YOUR PATIENTS

Table. Available insulins

Type of insulin	Trade name	Appearance	Timing of injection
Very quick acting (also known as analogue rapid acting insulin)	Humalog, NovoRapid, Apidra	Clear	Immediately before a meal
Quick acting (also known as short acting insulin)	Actrapid, Humulin-R	Clear	30 minutes before a meal
Intermediate acting (also known as isophane insulin)	Humulin NPH, Protaphane	Cloudy	At bedtime, breakfast or the evening meal
Long acting (also known as analogue basal insulin)	Lantus, Levemir	Clear	Does not need to be given with food
Premixed insulin			
Mixed quick acting and intermediate acting insulins	Humulin 30/70, Mixtard 30/70 and 50/50	Cloudy	30 minutes before a meal
Mixed very quick acting insulins*	Humalog Mix25 and Mix50, NovoMix 30	Cloudy	Immediately before a meal

* Biphasic formulations with the rapid onset of action of the very quick acting insulins but a duration of action similar to that of the intermediate acting insulins.

Giving the injection

It is important that you receive instruction on the technique of injecting insulin from someone who is familiar with the equipment you have chosen. Your local diabetes service can give you advice.

The general method of injecting insulin by pen or syringe is outlined below. Remember to use a new needle each time you inject. Each type of insulin pen has specific instructions on its proper preparation and handling. If you are using a pen, follow the instructions provided with it.

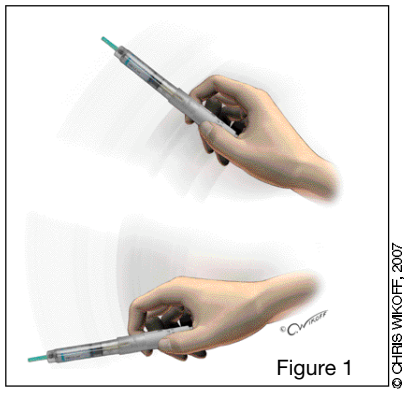

Figure 1

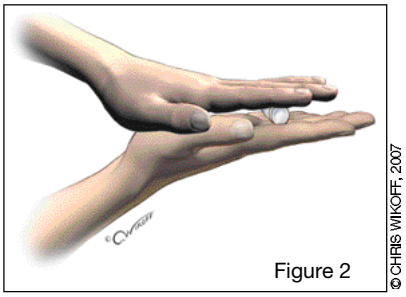

Figure 2

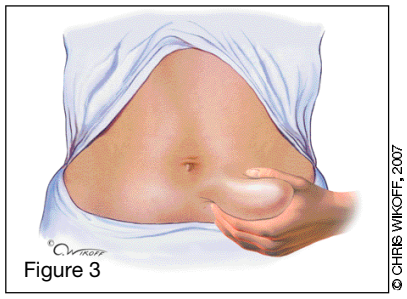

Figure 3

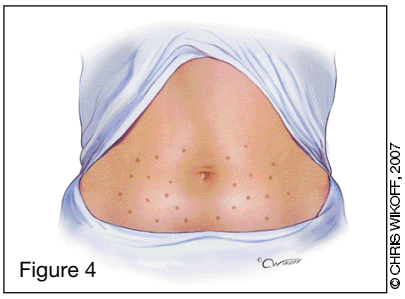

Figure 4

If you are using an insulin pen, follow these steps:

1. Ensure your hands are clean.
2. If you have been prescribed a cloudy insulin, mix it completely before each use. Don't shake the pen – instead, rock it backwards and forwards end to end, and then roll it between your hands (Figures 1 and 2).
3. Attach a new needle.
4. Dial up 3 units on the pen and push up the plunger to expel any air in the needle – look for a steady stream of insulin, not just drops.
5. Dial up your dose of insulin.
6. Pinch up an area on your abdomen, choosing a different site each time (Figures 3 and 4).
7. Put the needle into the pinched-up area at 90° – this is straight (Figure 5).
8. Press the plunger to inject the insulin and then hold the needle in place for 5 seconds.
9. Withdraw the needle.
10. Release the pinched up area.
11. Dispose of the needle as recommended.

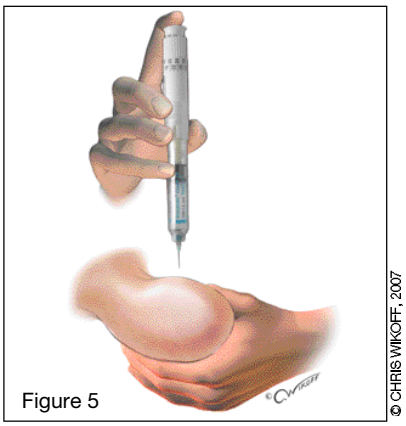

Figure 5

If you are using insulin in a syringe:

1. Ensure your hands are clean.
2. If you are using a cloudy insulin, mix it in the bottle as for a pen (step 2 above).
3. Remove the cover from the syringe needle and pull the plunger back to draw up an amount of air equal to the required dose of insulin.
4. Holding the insulin bottle upright, push the needle through the rubber stopper. Keeping the tip of the needle above the insulin, inject the air into the bottle by pressing the plunger.
5. Turn the insulin bottle and syringe upside down. Now the needle should be in the insulin. Pull the plunger back to draw the required amount of insulin into the syringe. Withdraw the needle from the bottle.
6. Inject the insulin as described in steps 6 to 11 above.

Disposal of syringes and needles

Used syringes and pen needles must be disposed of safely. Discard the syringe or needle into a puncture proof (strong plastic) container with a lid. Contact your local diabetes service, council or pharmacy for information about disposal facilities in your area – some provide special containers and arrange disposal. Never place used syringes in household garbage, and never leave an unused syringe unattended.

Storage of insulins

Store unopened insulin bottles and cartridges on their side in the fridge (between 2 and 8°C). Do not allow insulin to freeze; if it has frozen, it needs to be discarded because it may not work effectively.

Store opened insulin bottles and insulin pens loaded with insulin cartridges away from direct sunlight in a cool place, not in the fridge. Insulin is damaged by heat and so must not be kept in the car glove box or where the temperature exceeds 25°C, whether opened or unopened. Insulin must be used within 28 days of opening. Unopened bottles can be stored in the fridge until the expiry date; throw them away once they have expired.

Supply of insulin

You need a prescription from your doctor to obtain insulin. A spare bottle or cartridge of insulin or a spare prefilled pen should be kept on hand. Always check that the pharmacy and doctor have given you the correct type of insulin and that it is within its expiry date – check before leaving the pharmacy.

Supply of syringes

Register with the National Diabetes Services Scheme, administered by Diabetes Australia, for your supply of syringes and/or pen needles. Registration forms are available from your local doctor or State branch of Diabetes Australia (phone 1300 136 588; website www.diabetesaustralia.com.au).

My insulin

Keep a record of your insulin on the next page.

Remember to wear a medical alerting device such as a bracelet or necklace and to carry a card stating that you have diabetes and listing your medication.

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My insulin record		
Insulin	**Dose (units)**	**Time**
Name of insulin	*20*	*Before bedtime*

Notes

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Insulin therapy and air travel

This handout provides some guidelines for people with type 2 diabetes who are taking insulin and travelling by air.

Modified with permission from a resource produced by the Diabetes Centre, The Queen Elizabeth Hospital, Woodville, SA.

Guidelines for insulin adjustment during travel

When travelling by air, your place of departure and your destination may be in different time zones. If they are, you may need to adjust your insulin dosage on the day of travel to control your blood glucose levels before you adopt the 'local' time of your destination for meals and insulin injections.

If you are travelling across several time zones, it is advisable to keep following the local time of your place of departure until you arrive at your destination (i.e. don't change your wristwatch until you reach your destination) to keep track of your injections and meals. The length of time the flight takes has no effect on the time difference you will experience between the start and end of your journey because that time passes at both the place of departure and the destination.

The guidelines below will help you to adjust your insulin dosage, if you need to do so. You should discuss these adjustments with your doctor or diabetes nurse before your departure.

DIGITAL VISION / GETTY IMAGES

You may need to adjust your insulin dosages if you are travelling long distances by air.

The general rule

- If you are travelling to a time zone ahead of your local time, i.e. travelling east, your day of travel will be shorter than 24 hours and less insulin is needed.
- If you are travelling to a time zone behind your local time, i.e. travelling west, your day of travel will be longer than 24 hours and more insulin is needed.

If your day of travel is made shorter:

- by four hours or less (four or fewer time zones crossed), you should not need to make any changes to your insulin dose or food intake
- by more than four hours (more than four time zones crossed), you should reduce your insulin on the day of departure by 20 to 30%.

If your day of travel is made longer:

- by four hours or less (four or fewer time zones crossed), you should not need to make any changes to your insulin dose but you might need to eat extra carbohydrate (about 20 to 30 g, which is the equivalent of one to two slices of bread) to avoid low blood glucose before your next injection at your destination (following the local time at the destination)
- by more than four hours (more than four time zones crossed), you may need extra insulin and food to tide you over. Take your usual insulin on the day of departure up to your departure time and then have doses of quick acting insulin before the extra meals. Use 10% of your usual daily dose as an estimate; you can revise it up or down depending on your blood result at that time.

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Perform extra blood glucose tests

Whether your day is shorter or longer, do not be afraid to perform extra blood tests to keep track of blood glucose levels (every four to six hours is good). Remember that blood glucose measurements during the journey will probably be higher than normal because of your lack of physical activity.

Other travel tips for people with diabetes

- Plan your trip carefully, and find out about airline regulations on the carrying of diabetes supplies in your hand luggage and check-in luggage.
- During the flight, follow as closely as you can your normal insulin injections and meals and snacks, and make time for physical activity.
- Most airlines will make special arrangements for food for people with diabetes (remember to request this when booking your flight). You should, however, carry food with you, just in case. This food is part of the survival kit that you should have with you – the box on this page lists the items to include in this kit.
- Take several copies of a letter from your doctor stating that you:
  - have diabetes
  - take insulin (and other medications)
  - need to do blood tests
  - may need special arrangements for food and activity.

  Carry one copy of this in your hand luggage.
- Carry a full set of diabetes supplies (blood glucose meter and strips, insulin injectors and insulin) in your hand luggage. Also pack extra insulin and, if possible, a spare set of the other equipment in your check-in luggage.

Survival kit – type 2 diabetes

Carbohydrate

- Quick acting (high glycaemic index [GI]): glucose tablets, barley sugar or soft drink (not low calorie)
- Long acting (low GI): biscuits, dried fruit (e.g. sultanas)

Insulin

- Quick acting insulin (neutral) and syringes

Blood glucose testing equipment

- Meter, strips, finger pricker
- Tissues/cotton wool

Medical alert device or identification

Telephone numbers

- General practitioner
- Hospital clinic
- Ambulance

Further information

Diabetes Australia has information sheets on various aspects of living with diabetes, including travelling (*Travel and diabetes*) and coping with hypoglycaemia (*Hypoglycaemia and diabetes*). You can download these from the Diabetes Australia website (www.diabetesaustralia.com.au/education_info/sheets.html).

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