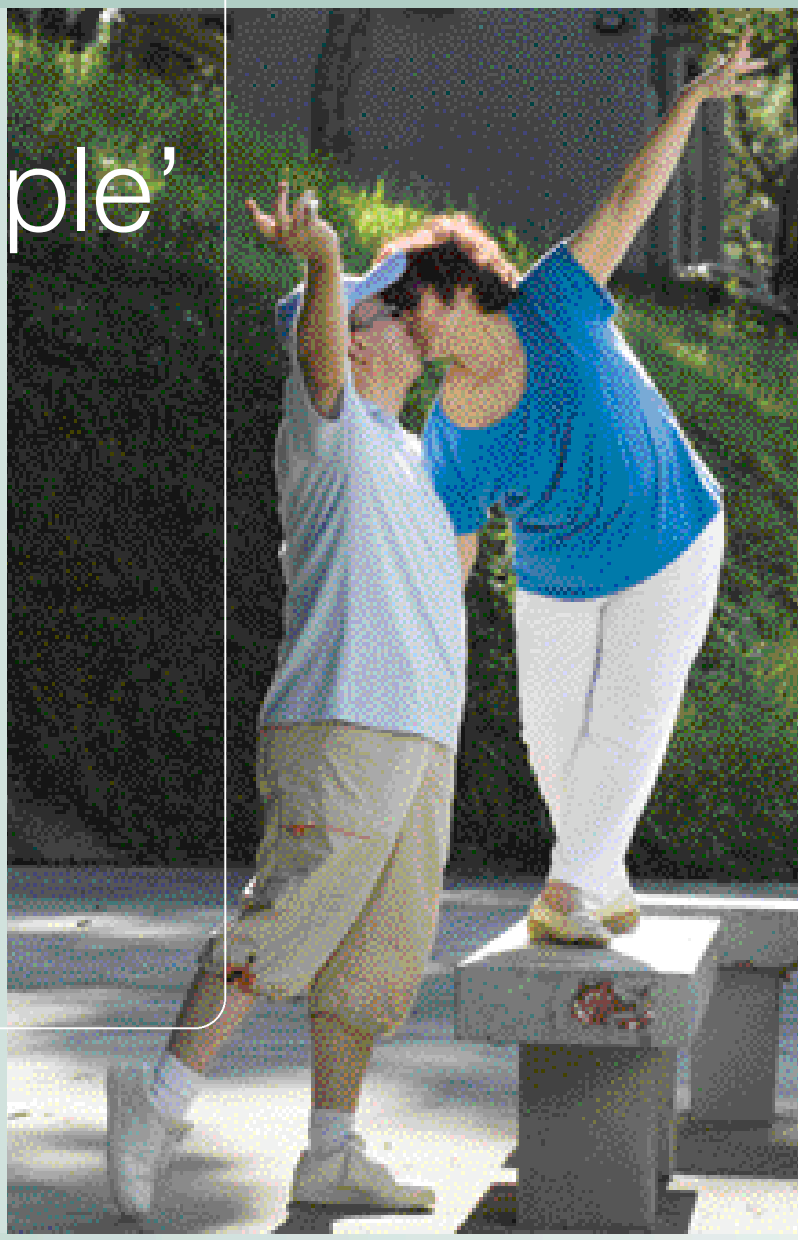
MedicineToday
The Peer Reviewed Journal of Clinical Practice

KISS-2: 'keep insulin safe and simple'

Reprint Collection



Foreword: The hypoglycaemic hierarchy in 2009

Psychogenic insulin resistance

Diabetes care – therapeutic inertia in doctors and patients

Six steps to a healthy lifestyle

KISS – getting A_{1c} under 7%

Insulin analogues – what do they offer to the insulin KISS?

The insulin KISS in older people with type 2 diabetes

Formerly MODERN MEDICINE

This supplement is sponsored as an educational service by **sanofi-aventis**

Reprint Collection – KISS-2
February 2009
ISSN 1443-430X

SYDNEY OFFICE
Level 1, 57 Grosvenor Street,
Neutral Bay, NSW 2089
POSTAL ADDRESS
PO Box 1473,
Neutral Bay, NSW 2089

TELEPHONE (02) 9908 8577
FACSIMILE (02) 9908 7488

EMAIL
Editorial enquiries
katemurchison@medicinetoday.com.au
Production enquiries
mariamarmora@medicinetoday.com.au
Advertising sales enquiries
irenaaleksoska@medicinetoday.com.au
General enquiries
reception@medicinetoday.com.au

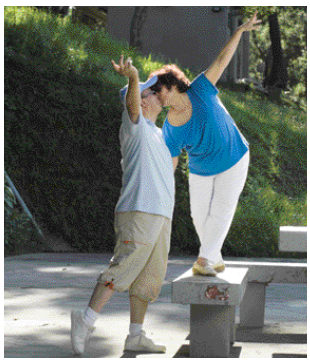
Medicine Today is a journal ofcontinuing medical education and review, written and refereed by doctors for GPs and specialists. The editorial objective is to provide authoritative clinical information that is useful and relevant to doctors in their day-to-day practice and to expand their medical knowledge. Editorial content is selected by the Editors, with advice from the Editorial Board of Consultants, with a view to providing readers with a broad spectrum of opinion on a wide range of subjects.
Opinions expressed are those of the original authors and do not necessarily reflect those of the Editors, the Editorial Board or the Publisher.
Medicine Today is published on the 1st day of each month by Medicine Today Pty Ltd (ACN 089 519 264).

Printed by Hannanprint Victoria,
504 Princes Highway,
Noble Park, VIC 3174.

SUBSCRIPTION RATES
Add 10% GST to all listed prices.

Standard	$180.00 per year, $310.00 for two years
Medical students	$80.00 per year, $140.00 for two years
RMO/Intern introductory offer	$90.00 per year $170.00 for two years
NZ, PNG, Fiji (Pacific region)	$215.00
Asia	$260.00
Rest of the World	$315.00
Back issues	$15.00 each $8.00 medical students $22.00 overseas

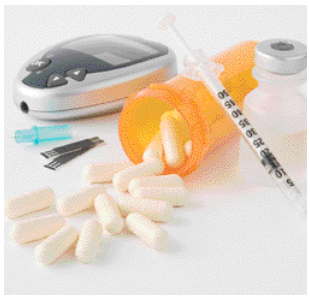
MedicineToday
The Peer Reviewed Journal of Clinical Practice



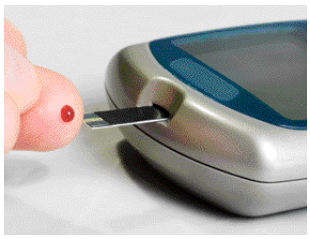
PHOTOLIBRARY

COVER

PAGE 4



PAGE 10



PAGE 22

The articles in this reprint collection were originally published in *Medicine Today*, July 2008 to January 2009. This collection has been sponsored by an unrestricted educational grant from sanofi-aventis. The opinions expressed in the articles are those of the author and not necessarily those of sanofi-aventis. Some products and/or indications mentioned may not be approved for use in Australia. Please review Product Information, available from the manufacturer, before prescribing any agent mentioned in these articles.

The hypoglycaemic hierarchy in 2009

Much has changed in the management of type 2 diabetes since the KISS series of articles started in the March 2007 issue of Medicine Today. In particular, the hierarchy of oral hypoglycaemic agents and insulin is very different now, in 2009, than it was then.

Before the glitazones became available in 2006, the recommendations for the management of patients with type 2 diabetes were a healthy lifestyle, then metformin and a sulfonylurea if tolerated and then insulin.

The introduction of the glitazones gave patients in whom metformin or sulfonylureas were not indicated or tolerated another oral hypoglycaemic option. Rosiglitazone could then be used as dual or triple therapy with a sulfonylurea, metformin and/or insulin, and pioglitazone could be used as dual therapy with metformin or a sulfonylurea or with insulin.

The glitazone glitch

In late 2007 and in 2008, concerns arose about the adverse effects of the glitazones. Rosiglitazone was reported to increase rates of myocardial infarction, and both rosiglitazone and pioglitazone were reported to precipitate heart failure, causing peripheral fractures and possibly causing or worsening macular oedema.

GLP-1 enhancers and mimetics

The roles of the gut, the pancreatic alpha cells and glucagon in controlling fasting and prandial metabolism are now firmly established, and medications have been developed that enhance or mimic the effect of the incretin glucagon-like peptide-1 (GLP-1) on fasting and postprandial blood glucose.

Sitagliptin is one of the new class of oral medications – the GLP-1 enhancers – that block the breakdown of endogenous GLP-1 by dipeptidyl peptidase-4. Exenatide, which is injectable, is a GLP-1 mimetic that binds to GLP-1 receptors. Sitagliptin has the advantage of having no effect on weight, and exenatide the advantage of being associated with weight loss.

The common side effects of these medications are nasopharyngeal congestion for sitagliptin and gastrointestinal problems (nausea, vomiting and diarrhoea) for exenatide.

At the time of publication, sitagliptin is PBS subsidised as dual therapy with a sulfonylurea or metformin if metformin or a sulfonylurea, respectively, is not tolerated.

The insulin KISS

There is now an international consensus on when and how to start and titrate insulin in type 2 diabetes: 'keep insulin safe and simple'. This KISS approach has become established and most Australian GPs have developed, or could develop, processes to start and titrate insulin in their patients with diabetes.

A_{1c} and CVD – is lower better?

Three recently published trials (ACCORD [Action to Control Cardiovascular Risk in Diabetes], ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation] and VADT [Veterans Affairs Diabetes Trial]) have shown no significant benefit of intensive over conventional treatment of glycaemia in terms of cardiovascular events. In one trial (ACCORD), cardiovascular mortality was increased in patients with intensive treatment and the trial was stopped early.

For the time being, the recommended Australian target for A_{1c} is less than 7%, but it is recognised that higher or lower targets may be appropriate for individual patients.

KISS-2

This second collection of articles (KISS-2) builds on the first collection (KISS-1), which focused on the practical issues of starting and titrating insulin.

Articles in KISS-2 review the barriers and psychological insulin resistance that patients and doctors have to overcome to embrace the insulin KISS; the need to 'eat less and walk more' when starting insulin to minimise the weight gain that would otherwise occur; and the pros and cons of insulin analogues compared with traditional insulin preparations. The final article in this collection stresses the importance of individualising glycaemic targets in older people and differentiating between the 'young old' and the 'old old'. The usual guidelines for insulin therapy are appropriate in the 'young old', but in the 'old old' intensive treatment can cause more harm and result in less benefit, and therapeutic caution may be more appropriate than therapeutic enthusiasm.

The KISS bottom lines

The bottom lines of the KISS approach have not changed:

- Insulin should be started sooner rather than later
- Start with a basal insulin and titrate to control the high fasting blood glucose level (BGL)
  'First fix the fasting'
- Check the BGL before the evening meal and, if necessary, address a high level
  'Then tackle tea'
- Check for high BGLs at other times of the day and address any high levels
  'Find the hidden hypers'
- Review overall glycaemic control
  'And check the A_{1c}'.

MT

PAT J. PHILLIPS FRACP, MRACMA, GradDipHealthEcon(UNE)
Senior Director, Endocrinology, North Western Adelaide Health Service, The Queen Elizabeth Hospital, Woodville, SA.

MedicineToday PEER REVIEWED ARTICLE MedicineToday 2008; 9(7): 33-40

Psychogenic insulin resistance

Insulin should be considered an expected step in the treatment of type 2 diabetes. Overcoming the patient's (and perhaps your) resistance to starting insulin is a major step in initiating insulin therapy.

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

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

Starting insulin can be perceived by both doctor and patient as indicating failure. Both can feel ashamed and/or blame the other for not controlling the diabetes. This is often a new experience for both and they may not feel up to the challenge. Insulin marks a transition from 'a touch of sugar' to something serious. 'Bad things happen to patients on insulin.' The doctor and the patient may feel that they are on their own and that they can't get practical support or advice.

No wonder there is 'therapeutic inertia' and patients and doctors delay starting insulin.[1]

Patient: 'No, no not yet.'

Doctor: 'Okay, we will give it one more try but then you will have to start'.

This article reviews some of the psychogenic barriers to progressing to insulin therapy in type 2 diabetes and briefly discusses a safe, simple and effective approach to initiating insulin therapy.

Failure

Patient: 'I had hoped that the new tablets would work but…'

Doctor: 'Now his tablets have failed…'

Diabetes can be seen as a whole series of failures.

First can be the sense of failure of getting type 2 diabetes. Everyone 'knows' that people get diabetes because they are 'fat, lazy, eat too much and don't look after themselves'. And people who get diabetes 'should know better' – after all their fathers (and/or mothers, brothers or sisters) got it so they 'should have tried harder'.

IN SUMMARY

- **Having to start insulin therapy in type 2 diabetes can be perceived by both doctor and patient as indicating failure in controlling the condition.**
- **Along with the failure may come shame and blame, a sense of inadequacy in dealing with the new challenge of starting insulin, and fear of perceived bad outcomes associated with insulin (weight gain, highs and lows causing comas, complications of sight and/or limb loss, loss of independence) and the pain of injections.**
- **The doctor and the patient both need a lot of help to start insulin therapy. They may have to work through their sense of failure and inadequacy and to face their fear of what starting insulin may be associated with.**
- **Once the doctor and the patient have accepted that insulin is an expected step in the treatment of type 2 diabetes, the KISS approach ('keep insulin safe and simple') is a simple and practical way of initiating insulin therapy.**
- **The essentials of the KISS approach are to start with one insulin preparation, one dose per day and one titration schedule and to initially target just one blood glucose level a day (usually the fasting level).**

Next can be the failure of lifestyle. The 'party line' is that 50% of people can control their diabetes by lifestyle change alone. Healthy eating and healthy activity make you and keep you healthy. When you don't succeed at all or when your blood glucose level increases again later you have 'obviously' not tried hard enough.

The Diabetes Attitudes Wishes and Needs (DAWN) Study showed that about half (55%) of people with diabetes feel that starting insulin means that they have not followed their treatment recommendations properly, and about one-third (36%) of their primary care physicians have been reported to agree with them.[2]

So far it is the patient who is doing the failing. However, doctors can feel that they have failed as well. The prescribed tablets are expected to work. Medications have been evaluated in scientific trials and Big Pharma promotes them by showing smiling, attractive people who are controlling their diabetes. The tablets don't always work: maybe they weren't the right ones, maybe they weren't started early enough, maybe the doses weren't increased quickly enough. The 'powerful' doctor has failed (and the patient shares some of the failure by still not trying hard enough to stick to healthy lifestyle habits or not reliably taking the pills).

Having to start insulin can be seen as the final failure and the biggest one. Now both the doctor and the patient feel they have failed each other badly. They have reached the end of the road. Now they can't go back, and thinking 'if only I had…' just makes it worse.

Of course, not all of the above is true. The points below, however, are true.

- Lifestyle change often does control newly diagnosed diabetes but only for a limited time. As a patient's insulin resistance progressively increases and insulin secretion progressively decreases, his or her blood glucose level progressively rises (Figure 1).
- Similarly, medications that reduce insulin resistance and increase insulin secretion will work initially, but as diabetes progresses so treatment will need to progress.
- Insulin therapy is not the end of the road. It is another step on the road. Insulin therapy is expected in type 2 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) showed that 50% of patients who start a sulfonylurea would require insulin within six years to keep blood glucose under control and A_{1c} below 7%.[3] With time, more and more people need insulin (Figure 2).[3] Although some studies suggest that newer oral hypoglycaemic agents may control blood glucose levels for longer, insulin will still be needed in a substantial number of patients with type 2 diabetes.[4]

Nonetheless, patients and doctors can feel as

Doctors and patients both have reservations about starting insulin

Failure
Patient: 'I had hoped that the new tablets would work but…'
Doctor: 'Now his tablets have failed…'

Shame/blame
Patient: 'I'm hardly eating anything, I'm walking 30 minutes every day and I still can't control it.'
Doctor: 'Mmm. His weight is up again, and so is his A_{1c}.'

Inadequacy
Patient: 'I don't like the idea of insulin. I'm not sure I can manage it all.'
Doctor: 'It's all getting so complicated these days.'

Fear
Patient: 'My father went on to insulin and was dead six months later.'
Doctor: 'What happens if he has a hypo while he is driving?'

Lack of support
Patient: 'They don't understand why I don't want to start insulin – they don't even try to.'
Doctor: 'Who can I ask who knows how to get started?'

continued

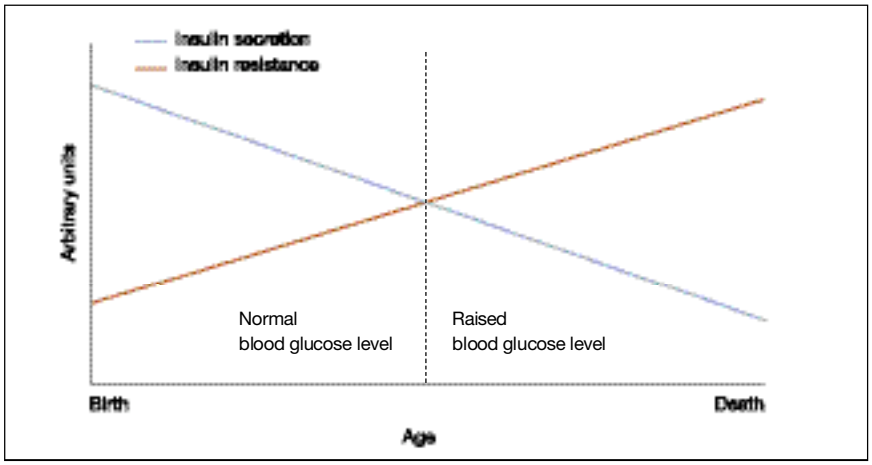


Figure 1. With increasing age, insulin resistance increases and pancreatic capacity to secrete insulin decreases. Initially, insulin secretion exceeds insulin resistance and the blood glucose level remains normal. However, after insulin resistance exceeds insulin secretion, the blood glucose level progressively rises with time.

though they have failed when, despite their best efforts, a healthy lifestyle and oral hypoglycaemics no longer control the diabetes.

Shame and blame

Patient: 'I'm hardly eating anything, I'm walking 30 minutes every day and I still can't control my weight.'
Doctor: 'Mmm. His weight is up again, and so is his A_{1c}.'

Along with the failure can come shame and blame. Diabetes itself is seen as a weakness, and in the past people hid their diabetes from others (even their family). Diabetes still hasn't fully 'come out of the cupboard'. Not being able to control the condition is perceived as showing a lack of willpower and commitment on the part of the patient, and inappropriate management on the part of the doctor – both are ashamed of the failure. Patients feel weaker still, and others blame them. Patients are told 'you are in control, you are responsible for your future health' and then they feel they aren't capable enough or strong enough to live up to these expectations.

As well as feeling ashamed and blamed for failure, both patients and doctors can often find someone else to blame – each other. Patients can also blame family, friends and work for not giving them a real chance. Australians are into 'naming and shaming' and the 'blame game' – diabetes gives us plenty of opportunities.

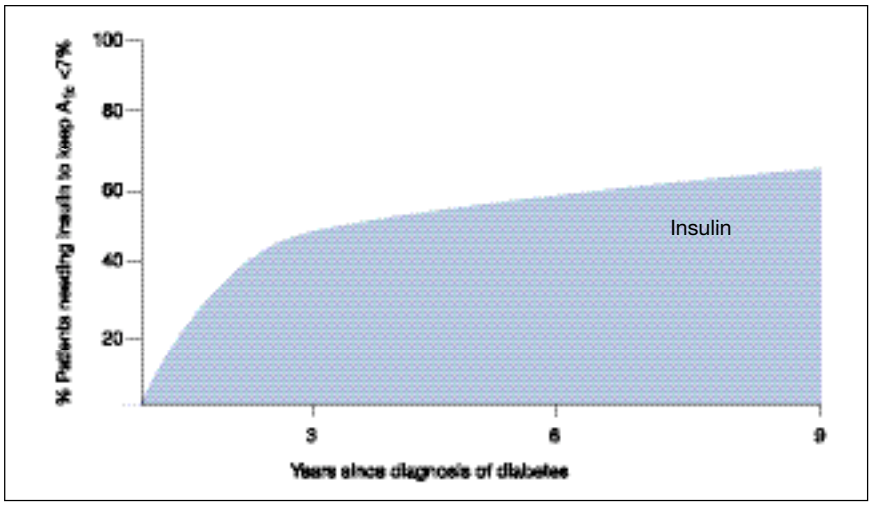


Figure 2. Treatment progression. With time, more and more people with diabetes need insulin to keep their A_{1c} below 7%.

Table 1. Numbers of medications taken by people with type 2 diabetes

Numbers of medications taken	Percentage of patients
0	18%
1	16%
2	14%
3	11%
4 to 6	24%
7 to 10	13%
More than 10	4%

Inadequacy

Patient: 'I don't like the idea of insulin. I'm not sure I can manage it all.'
Doctor: 'It's all getting so complicated these days.'

So far patients and doctors may be feeling that they failed, will be ashamed that they have not been able to control the diabetes and possibly may blame themselves, each other and other people.

These are big barriers, but there are more. Both patients and doctors see starting insulin as something complicated where they will need a lot of help and where the devil is in the detail. At the time of writing there were 20 different preparations of insulin and six injection

devices.[5] There were also at least five different schedules for giving insulin through the day, pages and pages of instructions on how, when and where to give the injection, lots of 'rules' on adjusting the doses of insulin, more 'rules' on what food to eat and not to eat and how much at what time, as well as the need to test blood glucose up to seven times a day.[5]

To cope with all this, the doctor may need to contact a specialist colleague and see the patient frequently or refer the patient to the diabetes specialist. The patient, apart from seeing the doctor and specialist, may need to see a diabetes nurse educator, a dietitian and perhaps an exercise physiologist to sort out the techniques and lifestyles skills needed to deal with the daily routines of living with insulin.

It can all seem too much. The doctor doesn't have time to sort it all out and the patient has enough on his or her plate already. Most patients are already taking many medications (Table 1),[6] seeing several health professionals, making many changes because of health problems, and spending large amounts of money. And they have the rest of their lives to get on with – job, family, friends, recreation, the footy, and so on.

Both patients and doctors may feel inadequate to deal with the new challenge of staring insulin therapy and this inadequacy may add to their sense of failure, shame and/or blame.

Fear

Patient: 'My father went on to insulin and was dead six months later.'
Doctor: 'What happens if he has a hypo while he is driving?'

Insulin therapy marks a major transition from what most people see as a small problem – a 'touch' of sugar 'only' requiring tablets – to a big problem that is so serious that it needs injections – several of them every day – to control it. Insulin can also be associated with all sorts of bad outcomes, such as getting fatter, large swings in blood glucose with 'highs' causing one form of coma and 'lows' causing another, and the complications that cause people to lose their sight, their limbs, their independence and their lives (Table 2). Insulin may also limit the user's driving, employment or recreation.

Doctors remember their student and junior doctor days, when the people with diabetes they saw in hospital were mostly on insulin, mostly end-stage and mostly way out of control. Patients remember and are reminded by 'helpful' friends and relatives that 'so and so' started insulin and shortly after had a heart attack, stroke or amputation, or needed dialysis or laser therapy. There are also stories about people losing consciousness or having fits or accidents because of hypos.

Moving from taking tablets, which most people in the general population do, to having daily injections, which very few do, forces patients and doctors to look more closely at the diabetes. They notice all sorts of things they have not seen, or chosen not to see, over the years. Now that 'touch' of sugar looks more like a disaster about to happen.

Then there are the fears that injections will be painful, that insulin will lead to addiction and that human insulin will cause AIDS, as well as various other problems that people generally associate with injections (Table 2).

Patients know they sometimes miss or double-dose their tablets – but what will happen if they miss their injection, the insulin doesn't work or they take too much. Many people with type 2 diabetes (48%) worry about insulin therapy well before they need to start.[2]

It helps for the doctor to be proactive. When the patient progresses to the maximum dose of oral hypoglycaemic agents, introduce the probable need to add insulin as the next step. Discuss the common fears patients have (Table 2). In particular, give the patient a 'dry' injection by inserting the needle of a syringe or pen injector through the patient's skin. Encourage the patient to repeat the procedure him or herself. Patients are invariably surprised that the injection is virtually painless, with nothing like the pain associated with finger-stick blood glucose testing.

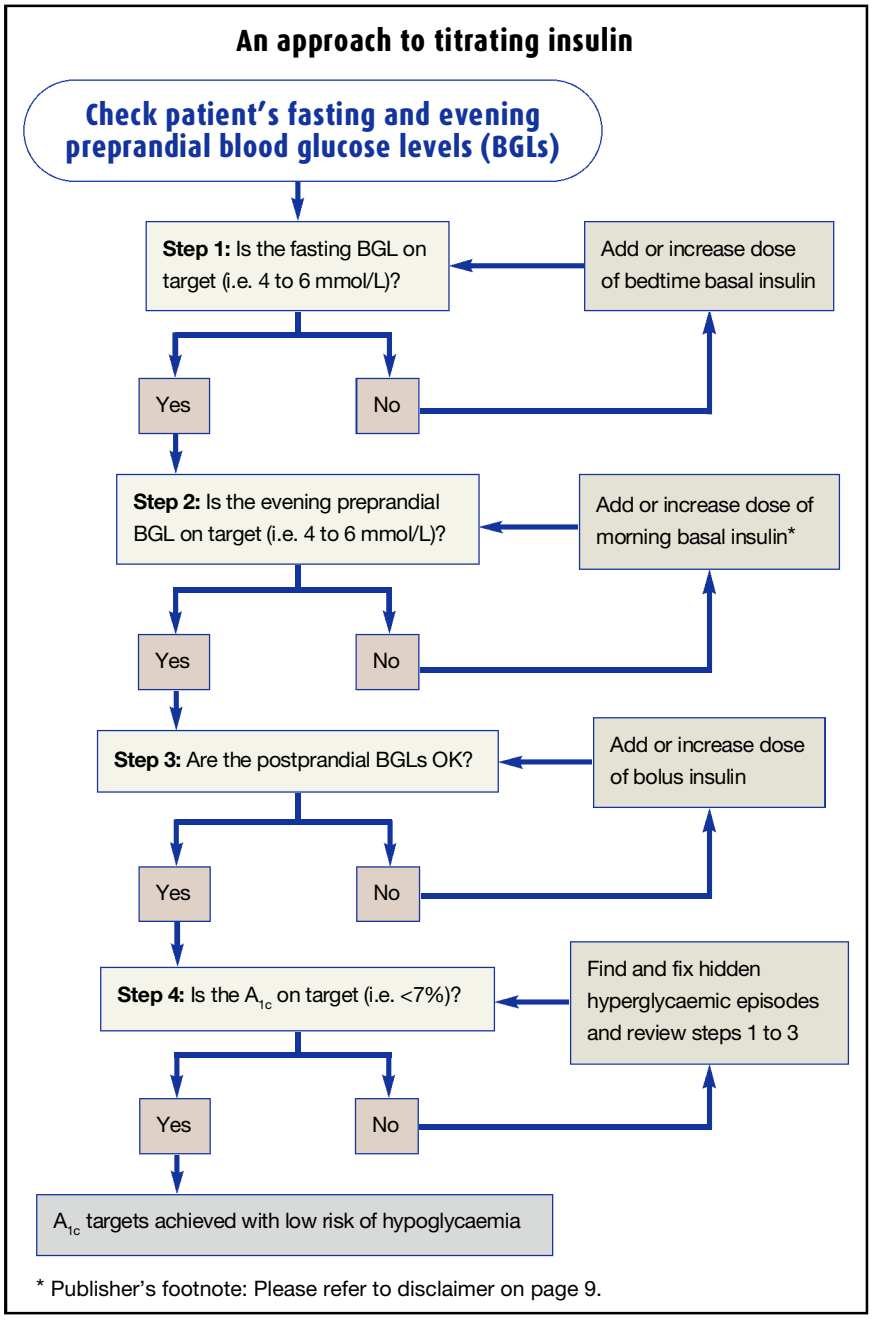
Lack of support

Patient: 'They don't understand why I don't want to start insulin – they don't even try to.'
Doctor: 'Who can I ask who knows how to get started?'

Table 2. Dealing with patient fears about insulin

Fear about insulin therapy	Explanation or action
Insulin will cause complications	Explain that insulin will improve diabetes control and thus reduce the risk of complications
Insulin will cause coma or loss of control	Explain that blood glucose control in type 2 diabetes is more stable than in type 1 diabetes and big swings are uncommon
Injection will be painful	Demonstrate that today's fine needles do not hurt
Human insulin will cause AIDS	'Human' insulin is manufactured and not derived from human tissue
Insulin treatment will lead to an 'addiction'	People with diabetes use syringes to inject the insulin because it cannot be taken by mouth as it is destroyed in the gut. There are millions of people taking insulin but they are not addicted to it

continued



* Publisher's footnote: Please refer to disclaimer on page 9.

The doctor and the patient both need a lot of help to start insulin therapy. The doctor has to decide what insulin schedule to prescribe, what to tell the patient and who to refer the patient to should this be necessary. The patient has to incorporate insulin and the changes it requires into his or her lifestyle and learn the required technical and other skills. They both have to work through their sense of failure and inadequacy and face their fear of what starting insulin may be associated with.

The doctor has less to cope with than the patient and is likely to have access to support from fellow medical and allied health professionals. Nonetheless, doctors may still feel the need for support but not be able to get it. The patient may have a partner who may share the burden. However, often the partner brings another set of problems, including fears about living with someone on insulin.

The Australian myth is of coping and getting on with it – giving it a go and knowing that 'she'll be right'. Real patients may feel overwhelmed by the prospect of insulin therapy and not have anyone to whom they can talk about their feelings, or know anyone they feel they could approach about this. Real doctors may feel overwhelmed by the challenge of persuading the patient to move on to insulin therapy and finding the necessary information and resources.

When faced with the prospect of starting insulin, both the patient and doctor may feel that they are on their own and can't get practical support or advice.

The KISS approach to starting insulin

The KISS approach ('keep insulin safe and simple') of initiating insulin starts with one insulin preparation, one dose per day and one titration schedule, and targets blood glucose level at just one time of the day.[7-10]

Once the first glucose level is 'fixed', the second is assessed and, if necessary, tackled. The long-term target is the A_{1c} (see the flowchart on this page). Starting is very easy:

- pick a basal insulin that has convenient injection devices
- decide which preprandial blood glucose level needs fixing (usually the fasting level but sometimes the evening preprandial level)
- start with 10 units of basal insulin and titrate according to the table in the box on page 9.[7,11]

The following jingle may make the KISS approach easy to remember:

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

Conclusion

The hardest task and the biggest step is deciding to start – overcoming the patient's (and perhaps your) psychogenic insulin resistance. Then it is a matter of a GP Management Plan (with or without a Team Care Arrangement) and accessing a nurse who can teach and support the patient. The nurse can follow up the patient and titrate the insulin according to the schedule you have set, and refer back to you once the targets are reached.

Once you have accepted that insulin is an expected step in the treatment of type 2 diabetes and put the KISS principle into your practice, you and your patients will feel much better. MT

Basal insulin titration[7]*

Start with 10 units of basal insulin. Adjust the dose twice weekly, to reach the target blood glucose level of 4 to 6 mmol/L, using the guidelines below:

Mean fasting glucose over preceding two 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 *Diabetes Care* 2003; 26: 3080-3086.[11]

References

1. Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension 2006; 47: 345-351.
2. Peyrot M, Rubin RR, Lauritzen T, et al. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 2005; 28: 2673-2679.
3. Wright A, Burden AC, Paisey RB, Cull CA, Holman RR. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS 57). Diabetes Care 2002; 25: 330-336.
4. Viberti G, Lachin J, Holman R, et al; for the ADOPT Study Group. A Diabetes Outcome Progression Trial (ADOPT): baseline characteristics of type 2 diabetic patients in North America and Europe. Diabet Med 2006; 23: 1289-1294.
5. Harris P, Mann L, Phillips P, Snowdon T, Webster C. Diabetes management in general practice 2007/8. 13th ed. Canberra: Diabetes Australia; 2007. Available online at www.racgp.org.au (accessed June 2008).
6. Grant J, Chittleborough C, Dal Grande E, et al. The North West Adelaide Health Study: detailed methods and baseline segmentation of a cohort along a chronic disease continuum. Epid Persp Innovations 2006; 3: 4.
7. Phillips P. KISS: 'keep insulin safe and simple'. Part 1: initiating insulin in type 2 diabetes. Medicine Today 2007; 8(3): 23-34.
8. Phillips P. KISS: 'keep insulin safe and simple'. Part 2: living with insulin and type 2 diabetes. Medicine Today 2007; 8(4): 43-54.
9. Phillips P. KISS: 'keep insulin safe and simple'. Part 3: troubleshooting insulin problems in type 2 diabetes. Medicine Today 2007; 8(5): 47-55.
10. Phillips P. KISS: 'keep insulin safe and simple'. Part 4: titrating insulin in type 2 diabetes. Medicine Today 2007; 8(6): 43-52.
11. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26: 3080-3086.

COMPETING INTERESTS: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.

MedicineToday PEER REVIEWED ARTICLE MedicineToday 2008; 9(9): 50-56

Diabetes care
therapeutic inertia in doctors and patients

One of the major barriers to best practice diabetes care is therapeutic inertia – failure to increase therapy when goals are unmet. An 'active' approach to routine diabetes care can greatly help in the control of complication risk factors and diabetic complications.

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

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

The next decade could see major improvements in diabetes care. New knowledge, new medications, new tests and new procedures give renewed hope for a cure. At the present time, however, the major goals in managing a person with type 2 diabetes – that is, the ABCss of diabetic care (controlling glycosylated haemoglobin A_{1c}, blood pressure and cholesterol levels [ABC], quitting smoking [s] and taking salicylates [s]) – are not being achieved. In fact, most people are missing most therapeutic targets; less than 1% are on target for all of them (Table 1).[1,2] This is despite current best practice in diabetes care being evidence-based,[1] with the interventions to improve complication risk factors and the medications used to achieve therapeutic targets having been demonstrated to be of value by large, appropriately designed and well-managed clinical trials (Table 2).[3-11]

This article explores one of the major barriers to best practice diabetes care and treating to target – therapeutic inertia in doctors and patients.

Therapeutic inertia – doctors

The definition for therapeutic inertia of 'failure to increase therapy when treatment goals are unmet' was proposed in a study of why blood pressure targets were not met.[12] This study identified that doctors were reluctant to increase antihypertensive medication. Predictors of therapeutic inertia in the study included older age, total number of medications and comorbidities such as cardiovascular disease, diabetes and dyslipidaemia.[12] All

IN SUMMARY

- **Therapeutic inertia – the failure to increase therapy when goals are unmet – is a major barrier to best practice diabetes care and treating to target in patients with type 2 diabetes.**
- **Most patients with type 2 diabetes are not achieving the targets of diabetes management (the ABCss – controlling glycosylated haemoglobin, blood pressure and cholesterol levels [ABC], quitting smoking [s] and taking salicylates [s]). Moving closer on all these targets has a dramatic therapeutic effect.**
- **Doctors should be active and insistent about achieving and maintaining target values of the main risk factors of diabetic complications, detecting problems early and intervening promptly.**
- **Patients should be informed about their diabetes and the required self-care and medical care, including adopting a healthy lifestyle, practising preventive care and, like doctors, being active and insistent about achieving and maintaining target values.**

these predictors apply to diabetes care so it is probably no surprise that the ABCss targets are being missed.

Perhaps doctors experience therapeutic inertia because the goalposts keep moving. For example, the target blood pressure has been reduced from 140/90 mmHg to 130/80 mmHg and is likely to go down further. Another example is the glycosylated haemoglobin (A_{1c}) target. However, although a lower A_{1c} level may be better for microvascular complications, the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial assessing the potential benefits of targeting blood sugar to near-normal levels (that is, the use of intensive therapy targeting A_{1c} to below 6% versus standard therapy targeting a level from 6 to 7%) was stopped because of excess mortality in the more intensively treated group.[13] Additionally, new medications may offer the promise of improvement but pose the practical problem of choosing between them on the basis of potential benefit and side effects.

Actually providing the care is also getting harder. The Medicare maze of acronyms (PIP, SIP, GPMP, TCA, HMR and so on), the paper chase and the endless red tape have to be overcome, and it can be hard work getting access to the Medicare Plus items for Allied Health resources.

It can also be hard to convince patients to increase therapy. Doctors may console themselves that 'It's pretty close… I'll check again next time… Anyway there are too many tablets already'.

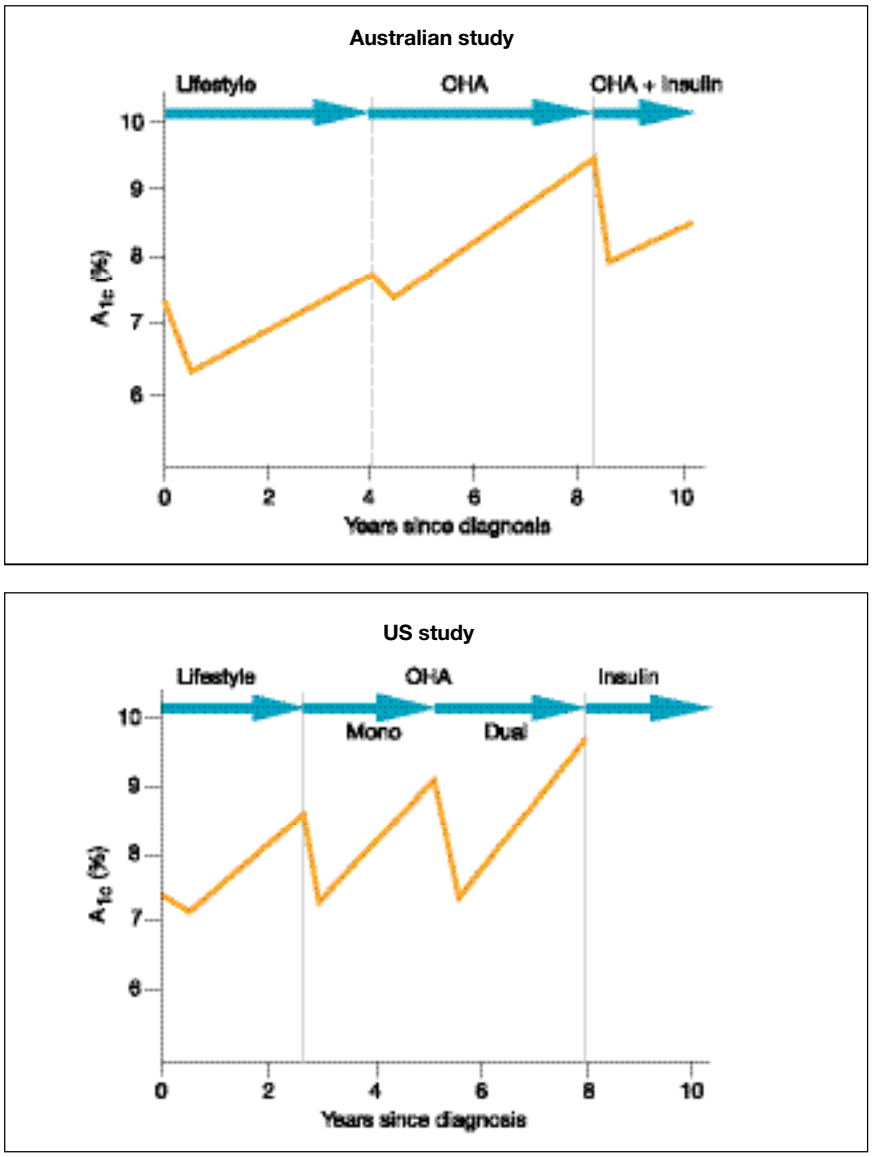
Australia is not alone in missing the targets in diabetes care. Patients with type 2 diabetes in Australia and the USA spend virtually all their time with A_{1c} values above the target of 7%, and a lot of time with A_{1c} values over 8% (Figures 1a and b).[14,15] These A_{1c} values are high, considering that average blood glucose level (BGL) in mmol/L is equivalent to $2A_{1c}$ minus 6, and therefore an A_{1c} of 7% equates to a BGL of 8 mmol/L whereas an A_{1c} of 8% equates to a BGL of 10 mmol/L. In both countries, increases in hypoglycaemic medication are delayed (therapeutic inertia) so each increase occurs at progressively higher A_{1c} levels.

A substudy of the United Kingdom Prospective Diabetes Study (UKPDS) has shown, however, that

Table 1. The ABCss of diabetic care – missing the targets

Diabetic care goal	Target[1]	Proportion of people with type 2 diabetes not at target[2]
A – controlling A_{1c}	<7%	54%
B – controlling blood pressure	<130/80 mmHg	71%
C – controlling cholesterol	<4 mmol/L	85%
s – quitting smoking	0	18%
s – taking salicylates	Aspirin 75 to 150 mg/day	61%

continued



Figures 1a and b. Therapeutic inertia in diabetes type 2. a (top). Australian study.[14] b (bottom). US study.[15] (OHA = oral hypoglycaemic agent.)

it is possible to get the A_{1c} on target.[16] In this study, intensive hypoglycaemic therapy (therapeutic 'ertia') showed that patients could spend virtually all their time with an A_{1c} below 7%. As the diabetes progressed, the hypoglycaemic medication progressed and kept the A_{1c} under 7% (Figure 2). The first oral hypoglycaemic agent was introduced at around the same time as happened in the US study but the second was added earlier (just after four years as opposed to five years) and insulin was started just after six years as opposed to approximately eight years.

Therapeutic inertia – patients

Theoretically, life with diabetes has never been better. The combination of self-care (healthy lifestyle, medication adherence and self-monitoring) and professional care (diabetes checks, tests and specialist referrals) can delay the onset and progression of micro- and macrovascular complications, but this is with the disadvantages of the hassle, expense and intrusion associated with self-care and professional care, and also weight gain and the side effects of medications. Patients are faced with the costs today but the benefits in the future are only potential and seem far away. Patients may not be prepared, in terms of time, energy, commitment and finance, to make the investment.

One simple health belief model suggests that patients will accept therapy if they agree to three key questions (personal communication, Stuart Dunn):

- Do I care?
- Will it work?
- Can I do it?

Table 2. Evidence for best practice diabetes care

- Control of A_{1c} – UK Prospective Diabetes Study (UKPDS) 33, 1998[3]
- Control of blood pressure – UKPDS 38, 1998[4]
- Control of cholesterol – Heart Protection Study (HPS), 2003[5] and Collaborative Atorvastatin Diabetes Study (CARDS), 2004[6]
- Quitting smoking – American Diabetes Association Standards of medical care in diabetes, 2008[7]
- Taking salicylates – American Diabetes Association Standards of medical care in diabetes, 2008[7]
- Using metformin – UKPDS 34, 1998[8]
- Using ACE inhibitors – Heart Outcomes Prevention Evaluation (HOPE) study, 2000[9,10]
- Using angiotensin-receptor antagonists – Prospective Epidemiological Study of Myocardial Infarction (PRIME), 2001[11]

Patients may have such a focus on living today that their health in 10 years' time is not an issue. They may not believe that diabetic care will deliver the promised benefits. After all, one-quarter of patients with diabetes will die of a cause that is not diabetes-related. Also, only half of the cases of diabetes complications are related to known risk factors, and these risk factors are hard to control anyway. Most of the medical risk factors are not controlled, and patients are not meeting lifestyle targets either.

The modern, middle-class mother has a career and job, her husband, children and other family, her friends, her garden and her house. She would find it hard to cope with yet another demand on her time, energy and commitment; diabetes would be a very unwelcome guest. The disadvantaged, unemployed, single mother has some of those same hassles but she may also have debt, no job, no money, no car, the threats of violence and eviction, and possibly trouble with the police. She has too much on her plate of life already, and would have great problems coping with diabetes as well.

Perhaps the answers to the three questions are:

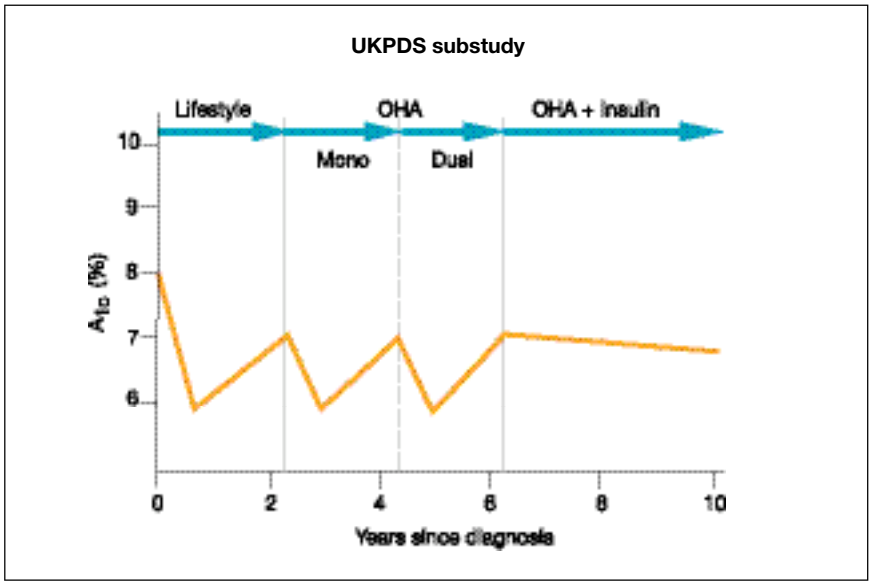
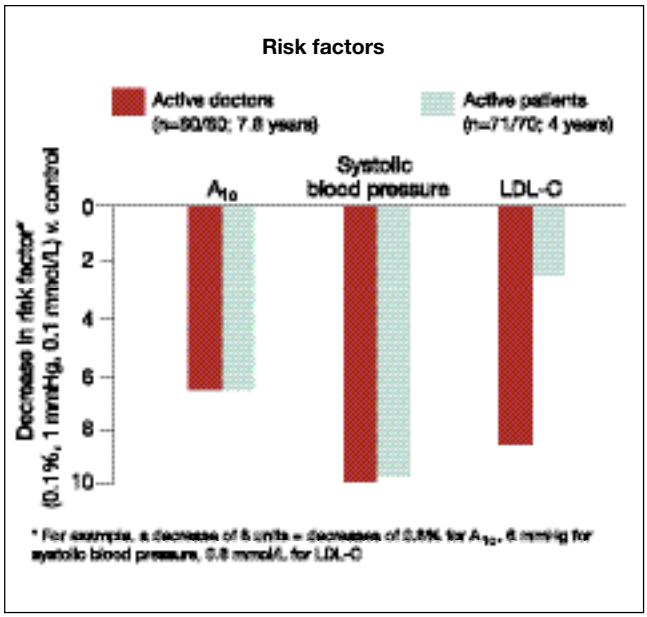


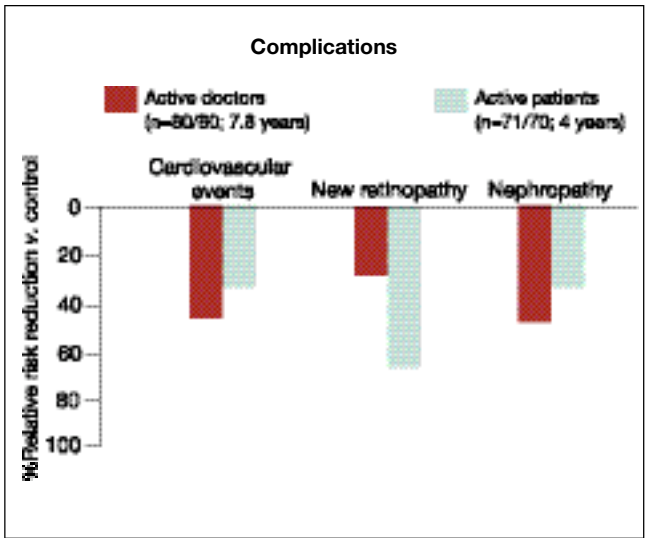
Figure 2. Therapeutic 'ertia' – UKPDS substudy.[16] (OHA = oral hypoglycaemic agent.)

- Do I care? – Somewhat
- Will it work? – Maybe
- Can I do it? – Probably not.

From inertia towards ertia

A Scandinavian trial (the Steno-2 Study) in high-risk patients with type 2 diabetes and microalbuminuria showed that an intensified, targeted, multifactorial intervention can make a major difference to both the risk factors for complications and the complications themselves compared with conventional treatment.[17] Although patients may not have achieved the ABCss targets with this 'active' approach by doctors, they did move closer to them. The combination of moving closer on all the ABCss targets had a dramatic therapeutic effect.





Figures 3a and b. Achievements of active doctors and active patients.[17,18] a (left). Risk factors. b (right). Complications.

continued

Diabetes care: active doctors and active patients

Diabetes care should be routine

There is an analogy between routine car maintenance and routine diabetes care.

- If you have a car, you fill it with fuel, check the tyres, oil, water and battery and arrange regular services.
  - If you are a mechanic, you service the car, do specific tests (e.g. brakes, timing) and refer to specialists (e.g. auto electricians, gearbox specialists).
- If you have diabetes, you take your medications, check your blood glucose level, feet, etc. and arrange regular diabetes checks.
  - If you are a doctor, you review diabetes care, check specific tests (e.g. fasting blood glucose level, urine tests) and refer to specialists (e.g. ophthalmologists, endocrinologists).

Active doctors

- Monitor risk factors, complications, specialist referrals and preventive care (e.g. immunisation).
- Intervene promptly when targets are not met and when complications occur.
- Assess adherence and response to interventions.
- Activate and support patient self-care.

Active patients[18, 19]

- Learn about diabetes and the required self-care and medical care.
- Try to make healthy lifestyle choices and to modify unhealthy lifestyle habits.
- Monitor eating, physical activity, blood glucose levels (and sometimes blood pressure).
- Be aware of the schedules for general practice and specialist reviews.
- Practise preventive care.
- Know the target values of the ABCss, the main risk factors of diabetic complications. These are:
  A – controlling A_{1c} to below 7%
  B – controlling blood pressure to below 130/80 mmHg
  C – controlling cholesterol to below 4 mmol/L
  s – quitting smoking (no tobacco)
  s – taking salicylates (75 to 150 mg aspirin per day)

When patients were given information about the targets to be achieved, how they could be achieved, what the potential benefits were and how to negotiate with their doctors and health care systems, similar remarkable improvements in complication risk factors and complications occurred (Figures 3a and b).[18]

As far as improvements in risk factors were concerned, active doctors did better than active patients in decreasing LDL-cholesterol levels but decreases in A_{1c} and blood pressure were similar (Figure 3a). For complications, active patients did better than active doctors in relative risk reduction of retinopathy and almost as well as active doctors in terms of cardiovascular events and progression of nephropathy (Figure 3b).

The effect of combining active doctors and active patients has not been demonstrated but could be expected to further improve control of complication risk factors and the complications themselves.

Conclusion

The message is clear for the doctors who provide the medical care and for the patients who provide the self-care and work with the diabetes care team: try even harder – be active and insistent about achieving and maintaining target values of the main risk factors of diabetic complications, detecting problems early and intervening promptly (see the box on this page).

Doctors may still not get all patients to meet all targets but targets can be moved closer to by steering away from inertia towards 'ertia', towards best practice and towards control of complication risk factors and diabetic complications. MT

References

1. Harris P, Mann L, Marshall P, Phillips P, Snowdon T, Webster C. Diabetes management in general practice 2008/9. 14th ed. Canberra: Diabetes Australia; 2007. Available online at www.racgp.org.au (accessed August 2008).
2. North West Adelaide Health Study. Population Research and Outcomes Studies: biomedical and self-report data. Adelaide: NWAHS; 2008.
3. United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in people with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-853.
4. UK Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317: 703-713.
5. Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes; a randomised placebo-controlled trial. Lancet 2003; 361: 2005-2016.
6. Colhoun HM, Betteridge DJ, Durrington PN, et al; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364: 685-696.

7. American Diabetes Association. Standards of medical care in diabetes – 2008. Diabetes Care 2008; 31 Suppl 1: S12-S54.
8. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-865.
9. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342: 145-153.
10. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000; 355: 253-259.
11. Lewis E, Hunsicker LG, Clark WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; 345: 851-860.
12. Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension 2006; 47: 345-351.
13. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545-2559.
14. Davis TM, Davis WA, Bruce DG. Glycaemic levels triggering intensification of therapy in type 2 diabetes in the community: the Fremantle Diabetes Study. Med J Aust 2006; 184: 325-328.
15. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. Diabetes Care 2004; 27: 1535-1540.
16. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999; 281: 2005-2012.
17. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348: 383-393.
18. Rachmani R, Levi Z, Slavachevski I, Avin M, Ravid M. Teaching patients to monitor their risk factors retards the progression of vascular complications in high-risk patients with type 2 diabetes mellitus – a randomized prospective study. Diabet Med 2002; 19: 385-392.
19. Phillips P (ed.). Diabetes and you: the essential guide. 2nd ed. Canberra: Diabetes South Australia; 2006.

COMPETING INTERESTS: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.

Six steps to a healthy lifestyle - the keystone in managing type 2 diabetes

PAT PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHealthEcon(UNE)
MELISSA CARAPETIS APD, BHSc, MND

Setting small, gradual goals can make it easier for patients with type 2 diabetes to attain a healthy lifestyle.

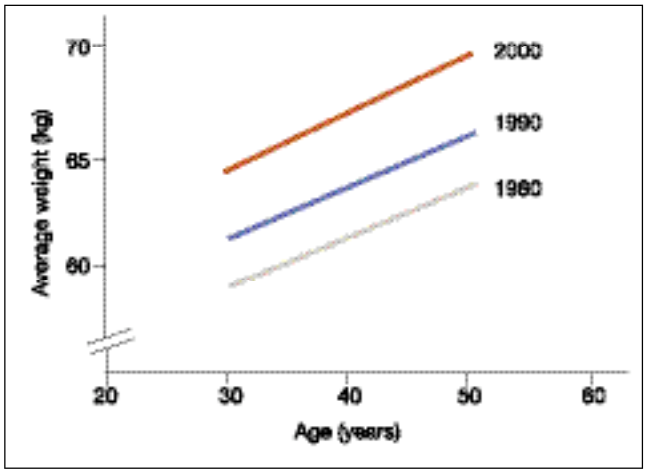


Figure 1. The increase in the average weight of Australian women aged 20 to 50 years from 1980 to 2000. As individuals we gain approximately 0.5 kg per year. As a nation the average Australian of any age gets fatter.

People with diabetes and their health professionals accept that having a healthy lifestyle is the keystone of diabetes management. But those people who have to adapt their lifestyle so it becomes healthy can find the necessary changes hard to accept. The 'healthy' choices are often hard choices and may require significant changes to the way people structure their day, do their shopping and cooking, and interact with friends and family.

This article outlines six steps to a healthy lifestyle and suggests a monitoring scheme to keep daily eating and activity on track.

Diet and exercise – too hard

'I know I should, but …'.

A diet is often perceived as a punishment, a deprivation and something imposed by an authority. People are told not to eat many of the foods they value and enjoy and to eat foods that they despise and dislike. As one patient put it, 'diet is die with a t'.

Dr Phillips is Senior Director, Endocrinology, at the North Western Adelaide Health Service, The Queen Elizabeth Hospital, and Ms Carapetis is an accredited practising dietitian at the Diabetes Centre, The Queen Elizabeth Hospital, Adelaide, SA.

Exercise often conjures up thoughts of muscular men and trim women jogging, cycling, doing aerobics and lifting weights; generally huffing and puffing and sweating. After all, 'no pain, no gain'. Many people have not done more than walk from the car park to the supermarket for years, and now they are expected to 'exercise'.

No wonder people with diabetes think that stopping eating the foods they like and starting activities they will find painful and embarrassing is 'too hard'.

And they are usually right. Most people do find it 'too hard' and cannot do it. Long-term adherence to, and success in, diet, exercise and weight-loss programs are rare.[1] After 12 months, most people have slipped back into their old habits and regained any weight they lost, plus the 0.5 kg per year that the average Australian gains (Figure 1).

Healthy lifestyle – easier

The goal sounds too simple – 'eat less and walk more'. If that is all there is to it why do most Australians gain weight and get less fit each year? People really can change their lifestyle. For many, the best approach is to try a series of achievable steps that add up to a significant and sustainable change over a one- to two-year time period.

The six steps to a healthy lifestyle

1. Aim for weight loss (or waist loss) if overweight

Most people with type 2 diabetes are either overweight or obese – that is, they have a BMI value of 25 kg/m^2 and over or 30 kg/m^2 and over, respectively.

No one likes to be told that they need to lose weight, but this is often the first advice given to patients once they have been diagnosed with diabetes. The benefits of weight loss can be great for someone with diabetes, including decreased insulin resistance, improved glycaemic control, improved blood lipids and reduced blood pressure.

The good news for patients is that even modest weight loss of about 5% of starting weight can be beneficial.[2] Encourage patients to set weight-loss goals. Refer them to local support programs and dietetic services. Community health centres and councils often have information about lifestyle programs in the local community.

Focusing on 'waist loss' rather than 'weight loss' is another useful approach,

Waist circumference

For men

Healthy waist: under 94 cm
Over waist: 94 to 102 cm
Very over waist: over 102 cm

For women

Healthy waist: under 80 cm
Over waist: 80 to 88 cm
Very over waist: over 88 cm

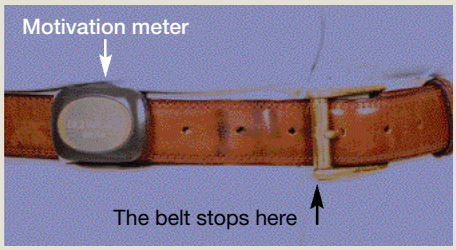


Figure 2. A 'belt lifestyle monitor'.

Tips for taking an accurate patient waist measurement

- Measure directly over the skin if possible (or over light clothing)
- Take the measurement after patient exhales normally
- The tape measure should be firm but not tight and kept parallel to the floor
- Keep the tape measure at the mid-way point from top of hip bone and bottom of lowest rib (roughly in line with the navel)

Tips for eating less

- Drink a glass of water before eating and with your meal
- Use a smaller plate
- Eat slowly
- Chew your food many times
- Put your fork down between mouthfuls
- Sit down while eating
- Eat with others and discuss the food you are eating
- Eat away from distractions (such as the television) and take time to savour your food
- Freeze left-overs straight away or only make enough food for one meal

especially for people who are reluctant to step on the scales. Waist circumference is a valid measure of abdominal fat mass and disease risk.[3] Both men and women should lose some of their waist so that their belt fastens on a few notches smaller. Ideally, men should have a waist circumference of less than 94 cm and women, less than 80 cm (see the box above).

2. Eat less food

Most people eat not because they are hungry but because it is a mealtime or snacks are easily available. There is the tendency for people to keep eating until they are full and to think it is rude not to clear the plate or to refuse seconds or dessert. They may eat large amounts of food while they are watching TV and not even wait until they have finished one mouthful before taking the next. Often they do not even enjoy their food.

Some tips for eating less food are outlined in the box on this page.

3. Eat less energy-dense foods and drinks

The 'big three' energy foods are fat, alcohol and added sugar (sucrose), weighing in at approximately 36, 28 and 16 kJ/g (9, 7 and 4 kcal, respectively). Food and drink high in these three ingredients are the so-called 'empty foods' that provide energy but often not many other nutrients. Encourage people to find the fat, seek the sugar and assess the alcohol in their daily intake. All three can be easily identified and there are palatable ways to reduce fat and added sugar in foods, both during food preparation and at the table.

People with diabetes are advised to seek lean low-fat red meats as sources of iron and low-fat dairy products as sources of calcium. Soy milk products are low in calcium unless fortified.

Some fats are better than others. Saturated and trans fats are associated with increased LDL-cholesterol and cardiovascular risk, while mono- and polyunsaturated fats (omega-3 and omega-6 fats) improve the lipid profile and decrease cardiovascular risk.

Many animal foods and processed foods are high in saturated and trans fats, as are some vegetable oils (such as coconut and palm). Food sources of saturated and other fats are listed in Table 1.

Food labels list the ingredients of foods, and people can learn to identify foods likely to be high in saturated or trans fat and/or high in added sugar, and then their healthier alternatives. Table 2 is a guide of what to look for on the nutrition panels of food labels.[4]

The 2008 draft NHMRC Alcohol Guidelines advises no more than two standard drinks per day (20 g) for all Australians, a reduction for men but not for women from the previous recommendations.[5]

4. Eat low-GI carbs

It is recommended that 45 to 65% of food energy be provided by carbohydrate.[6] Carbohydrate foods with a low glycaemic index (GI) release glucose more gradually and may cause lower postprandial blood glucose values.[7] The slow release of glucose may also reduce the risk of hypoglycaemia between meals for those on insulin or sulfonylurea therapy. Because low-GI foods are generally more filling than high-GI alternatives, people may find it easier to limit their total intake. Examples of low-GI foods include wholegrain breads, legumes and fruits such as apples and pears. Some low-, moderate- and high-GI

continued

Table 1. Types of fats found in foods

Unhealthy fats

Saturated and/or trans fats

Fats

Butter, lard, copha, cooking margarine, hydrogenated margarines, ghee, dripping, dairy blends, vegetable shortening

Cream, sour cream

Fatty meats

Chops, poultry skin, chicken wings, fatty mince, fatty pork

Smallgoods (sausages, saveloys, fritz/devon, salami, bacon, mettwurst)

Paté

Full-fat dairy products

Milk, cheese, cream cheese, yoghurt, ice cream

Plant sources

Coconut oil, cream and milk

Palm oil (used in many fast foods, takeaway foods, cakes and biscuits)

Toasted breakfast cereal, e.g. muesli

Takeaway foods

Commercial cakes, pastries, biscuits and chocolates

Deep fried or battered foods

Pies, pasties, sausage rolls

Pastries – shortcrust and puff pastry

Potato crisps, hot chips

Healthy fats

Monounsaturated fats

Oils and margarines

Canola*

Olive

Macadamia

Sunola (a sunflower oil high in oleic acid)*

Peanut

Vegetables

Avocados

Olives

Nuts

Almonds

Peanuts, peanut paste

Cashews

Hazelnuts

Macadamias

Pecans

Polyunsaturated fats

Oils and margarines

Sunflower

Safflower

Corn

Soybean*

Sesame

Cottonseed

Grapeseed

Linseed (also known as flaxseed oil)*

Nuts and seeds

Walnuts*

Pine nuts

Brazil nuts

Sesame seeds

Sunflower seeds

Linseeds*

Fish and other seafood

Canned: Sardines*, salmon*, mackerel*

Fresh: Atlantic salmon*, tuna*, mullet*, gem fish*, trevally*, snook*, flathead, calamari*

* Good sources of omega-3fats.

foods are listed in Table 3.[8]

Low-GI foods are often higher in fibre, particularly soluble fibre. Soluble fibre forms a gel that slows gastric emptying and intestinal nutrient absorption. It can increase satiety, slow the rate of starch digestion and lower LDL-cholesterol. Insoluble fibre passes through the colon unchanged, increasing stool weight by its own mass and by its ability to hold water. Fibre increases bulk, softens the stool and can increase the regularity and comfort of passing stool.

Most Australians only eat one-third of the recommended fibre intake. Fibre intake can be increased by replacing nutrient-poor energy-dense foods and drinks with vegetables, fruits and wholegrain cereals.[8]

Fruit and starchy vegetables vary greatly in their GI but the national 'Go for 2&5' campaign (two fruit and five vegetables) is important regardless of GI because of the many benefits provided by fruit and vegetables. One serve of fruit is equivalent to one medium sized piece (such as an apple) or two smaller pieces (such as apricots), and one serve of vegetables is equivalent to half a cup of cooked vegetables, one medium potato or one cup of salad vegetables. More information is available on the 'Go for 2&5' website, www.gofor2and5.com.au.

There are many GI checklists to help people identify high-GI foods and their lower GI alternatives.[7] Although the GI of a food is important, the glycaemic response depends more on the amount of carbohydrate in the food.[9] A high carbohydrate intake, even if low GI, is likely to cause unwanted spikes in postprandial blood glucose levels. An excessive amount of carbohydrate has also been linked to elevated triglyceride levels.

In recent years, several dietary plans have emerged based on lower carbohydrate intakes than traditionally recommended. The popular and evidence-based CSIRO Total Wellbeing Diet is one such diet.[10] In these diets, either protein or monounsaturated fat replace some of the energy from carbohydrate. These diets may be an effective approach to both weight and diabetes management. People with diabetes who are following these diets and are on insulin therapy or taking insulin secretagogues may need to adjust their medication dosages to match their carbohydrate intake. A dietitian referral might be useful in this scenario.

5. Watch the salt

A diet high in salt can contribute to hypertension, oedema, heart disease and kidney disease. Reducing sodium intake is an important dietary goal for all, but perhaps

even more so for people with diabetes because they have higher rates of sodium-related medical conditions.

There is a period of adjustment when reducing sodium intake. Once again, gradual changes are usually easier. Encourage patients to focus on reducing sodium intake from processed foods, since this makes up 75% of most people's total sodium intake. Remind them that sodium is not only from salt added during cooking or at the table, but also from salt added during the manufacture of processed foods and also from other sodium-containing ingredients such as monosodium glutamate, baking powder and sodium bicarbonate. Advise people to look for food products with less than 400 mg of sodium per 100 g, and less than 120 mg per 100 g where possible.[11]

Table 2. Healthy foods: checking the food label nutrition panel

Nutrient	Per 100 g*
Fat	
– Total	Aim for less than 10 g per 100 g For milk and yoghurt, aim for less than 2 g per 100 g Oils and margarines are all high in total fat (more than 10 g per 100 g); choose polyunsaturated and monounsaturated varieties
– Saturated	Aim for as low as possible
– Trans	Aim for as low as possible For margarines, aim for less than 1 g per 100 g
Carbohydrate	
– Sugars	Aim for less than 10 g per 100 g For foods containing fruit, aim for less than 25 g per 100 g
Dietary fibre	For breads and cereals, aim for more than 5 g per 100 g (the recommended daily intake is 30 g)
Sodium	Aim for less than 400 mg per 100 g, and if possible less than 120 mg Look for 'no added salt', 'salt reduced' and 'low salt' labels

* Remember to look at the 'per 100 g' column, not the 'per serve' column.

6. Exercise regularly

'The hardest thing is putting on my joggers' – John training for a city fun run.

Our grandparents walked much more than we do now – the equivalent of a marathon (42.2 km) or more each week. Our activity progressively decreases as we get older. Most Australians with type 2 diabetes are over 50 years of age and in a low-activity group in a low-activity population. As a nation, we pride ourselves on our Olympic performance; but as individuals, most of us are 'couch potatoes' (Figure 3).

Getting started is usually the hardest part if activity is not part of someone's daily schedule. When people do start, they may embark enthusiastically and hurt themselves. They may set unrealistic goals and then feel frustrated and disappointed. They may try and 'fail' several times and then give up for good.

Suggest to patients that they find something they enjoy, set an achievable goal and start slowly. Most people walk when they want to increase their activity. Some people find a pedometer helps them keep on track – it gives them a benchmark that they should try and achieve each day and build on every week. The guidelines listed below may be helpful:

- set the basal daily target at the current level of activity (number of steps)
- each week increase the daily target by 10% (e.g. 2000 steps to 2200)
- do this for a month then review the number of steps, the possibility of further increases and the commitment to increasing activity
- repeat the increasing activity process until a desired and/or desirable daily target is reached
- maintain the activity, meeting the daily target
- each year – birthdays and New Year are good times – review activity and consider increasing current activities and/or adding new ones.

A commonly quoted target for a healthy level of activity is the 10,000 steps per day adopted by Queensland Department of Health (www.10000steps.org.au). This goal may seem ambitious to many people whose current activity equates to 1000 to 3000 steps a day (a fairly representative activity level). However, starting at 2000 steps a day and increasing 10% each week will lead to 5000 steps in four months and 10,000 steps in six months. If weekly increases are too much, increasing second-weekly will get to 10,000 steps over one year.

Encourage extra incidental activity. For example, when parking take the first space you see and walk, don't cruise and look for closer ones; cancel the milk and paper orders and walk each morning to the shop instead; take the stairs and not the lift; and walk up and down the escalator. Remind patients to think of movement as an opportunity, not an inconvenience.

Those people who may find it too dangerous, unpleasant or uncomfortable to be active outdoors can participate in a physical activity at home. They can use a walking/jogging machine or a stationary bike, and can even read a book, watch television or listen to music while doing so. Most people spend a lot of time watching television so there is

continued

Table 3. The GIs of some carbohydrate-containing foods

Low-GI foods (GI, 55 or less)

Breakfast cereals
Generally rice bran, oat bran, porridge oats*
Specific cereal brands: Kellogg's All-Bran (all varieties), Kellogg's Guardian, Kellogg's Guardian Oat Puffs, Burgen Muesli (Fruit and Muesli, Rye, Soy Lin), Natural Muesli, Kellogg's Komplete, Freedom Foods Hi-Lite Cereal
Also: semolina (cooked)

Breads and cereals
Generally wholegrain and multigrain breads*
Specific bread brands: Tip Top 9 Grain bread and muffins, Burgen Fruit and Muesli bread, Burgen Rye bread, Burgen Soy-Lin bread, Burgen Wholemeal and Grain bread, Wonder White Low GI sandwich bread, Vogel's Original Mixed Grain, Vogel's Seven Seed, Vogel's Soy and Linseed with Oats, Continental fruit loaf
Also: pearl barley, pasta (white and wholemeal), cracked wheat (bulgur), buckwheat, rice noodles (fresh, boiled), Sunrice Doongara Clever Rice, Maggi 2 Minute Noodles

Biscuits
Specific biscuit brands: Ryvita crispbread (Pumpkin Seeds and Oats, Sunflower Seeds and Oats), Snack Right Fruit Slice, Freedom Foods Fruit Cookies (Apricot Temptation, Blueberry Bliss)

Vegetables
Sweet corn, sweet potato (baked), taro, yam

Legumes and pulses
Lentils, kidney beans, split peas, chick peas, baked beans

Dairy products
Yoghurt, milk, custard – choose low-fat varieties

Fruit
Grapefruit, dried apricots, fresh and dried apples, pears, plums, peaches, oranges, grapes, banana (average size), prunes, mango, kiwifruit

Spreads
Jam (100% fruit)

Juices
Fruit juices† (apple, orange, pineapple, grapefruit)

Moderate-GI foods (GI, 56 to 69)

Breakfast cereals
Specific cereal brands: Sanitarium Weet-Bix, Uncle Toby's Vita Brits, Kellogg's Special K, Kellogg's Just Right, Kellogg's Mini Wheats (wholewheat)
Also: porridge (regular oats with water)

Breads and cereals
Light rye bread, pita bread (white), crumpet, croissant‡
Specific bread brands: Helga's Classic Seed Loaf, Tip Top Multigrain Sandwich bread
Also: couscous, basmati rice (white, boiled Mahatma), Ricegrowers Doongara rice (white/brown), Sunrice Arborio risotto rice (boiled), wild rice (boiled), dried rice noodles (boiled), gnocchi

Biscuits
Digestive biscuits‡
Specific biscuit brands: Jatz‡, Ryvita crispbread (Original Rye, Sesame Rye), Shredded Wheatmeal, Milk Arrowroot

Fruit
Sultanas, pineapple, rockmelon, apricots, cherries, raisins

Sugars
Sugar (sucrose)

High-GI foods (GI, 70 to 100)

Breakfast cereals
Specific cereal brands: Sanitarium Puffed Wheat, Kellogg's Rice Bubbles, Kellogg's Sultana Bran, Kellogg's Bran Flakes, Kellogg's Corn Flakes, Kellogg's Coco Pops, Kellogg's Mini Wheats Blackcurrant, Uncle Toby's Instant Porridge (made with water)

Breads and cereals
Generally white and dark-rye breads, bagels (white), baguettes, rice cakes
Specific bread brands: Helga's Traditional Wholemeal bread, Tip Top Hyfibe White sandwich bread
Also: tapioca, jasmine rice (Sunrice)

Vegetables
Potatoes (most white varieties), broad beans

Biscuits
Water crackers, Sao‡, Morning Coffee

Fruit
Watermelon, dried dates, canned lychees

Snack foods
Pretzels

Drinks
Sports drinks, Lucozade

Sugars
Malt (maltose), glucose, jelly beans

* Not all brands may be low GI.
† These foods are low in fibre.
‡ These are foods high in fat – eat only occasionally.

plenty of opportunity to use an exercise machine.

Any extra activity is better than none, but aiming to walk 'two to three times per week' may work out to be twice a week, then once a week, then once every now and again. Adopting the approach 'you only have to take exercise regularly, not seriously' encourages participation as it suggests that exercise should not be regarded as a special activity. Help patients make a commitment to make activity a part of every day by suggesting they establish a specific time of the day for activity so that they do not keep putting it off. Often in the morning before breakfast and in the evening before or after the evening meal are good times. Local councils and community health centres usually have information on opportunities for enjoyable activities in the local area.

Some patients will be motivated by written instructions, and GPs may write exercise prescriptions as recommended by

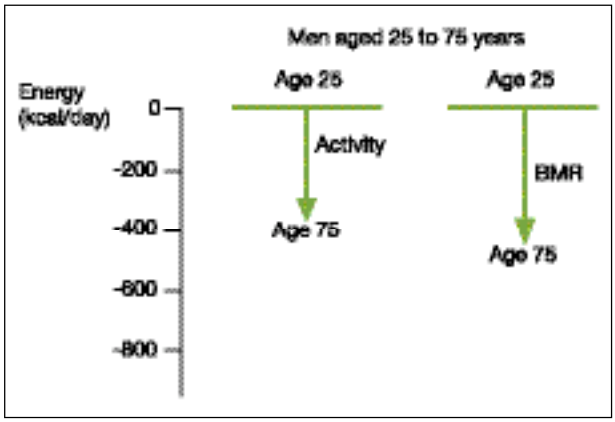


Figure 3. As we age we are less active as well as having a lower basal metabolic rate (BMR). This is equivalent to a reduction of 400 kcal/day in terms of activity and 500 kcal/day in terms of BMR.

the National Heart Foundation.[12] The RACGP provides some useful tips or health promoting behaviour as part of the SNAP framework (Smoking, Nutrition, Alcohol and Physical activity).[13] Also, people with type 2 diabetes are entitled, under a Team Care Arrangement, to five allied health visits per year under the Medicare scheme. Referral to an exercise physiologist (accredited by the Australian Association for Exercise and Sport Science) is included within this scheme. Exercise physiologists are exercise specialists with the knowledge and skills to design and deliver general physical activity advice and clinical exercise prescriptions for healthy people and those with chronic and complex diseases.

Monitoring lifestyle

People who succeed and persist in lifestyle change are often the ones who monitor their eating, activity and weight/waist. Tools include food checklists, meal plans, calorie counters, food and activity diaries, a pedometer and a tape measure. As measures of daily activity, pedometers make it harder for people to persuade themselves that they have been 'so busy' and feel 'so tired' that they must have done enough activity. Tips on how to measure waist circumference accurately are given in the box on page 17. Motivated patients may use their belts as their lifestyle monitor – the buckle monitors waist circumference and gives a clear indication of long-term overall energy balance, as long as the belt is positioned around the belly and not beneath it (see Figure 2 in the box on page 17). The pedometer gives them feedback in terms of their activity level.

Joining support groups and walking groups and seeing a dietitian helps patients maintain commitment to lifestyle change and maintenance of that change, as well as providing social interaction and peer support.

It is easy to change for a day or a week, but changing and maintaining change long term can be difficult. Encourage people to set goals and monitor their progress. These behaviours can help them make and maintain lifestyle change.

Summary

Changing lifestyle can be difficult for patients but setting small, gradual goals can make it easier. Encourage patients to work towards the 'six steps to a healthy lifestyle' one at a time, as described below.

- Step 1. Lose weight/waist
- Step 2. Eat less food
- Step 3. Eat less energy-dense food
- Step 4. Eat low-GI carbohydrates
- Step 5. Watch the salt
- Step 6. Walk more.

Where possible, provide support and access to resources, not just advice. Monitor how your patients are progressing with their six steps and encourage them to monitor and track their own progress. MT

References

1. Tsai AG, Wadden TA. Systematic review: an evaluation of major commercial weight loss programs in the United States. Ann Intern Med 2005; 142: 56-66.
2. American Diabetes Association. Nutrition recommendations and interventions for diabetes. A position statement of the American Diabetes Association. Diab Care 2008; 31(Suppl 1): S61-S78.
3. Dietitians Association of Australia (DAA). Best practice guidelines – treatment of overweight and obesity in adults. Canberra: DAA; 2005.
4. Phillips P, Carapetis M, Stanton C. How to read food labels. Med Today 2007; 8(1): 61-66.
5. NHMRC. Draft Australian alcohol guidelines for low-risk drinking. Canberra: Commonwealth of Australia; 2008. Available online: www.nhmrc.gov.au/guidelines/consult/alcohol_guidelines.htm (Accessed July 2008).
6. NHMRC. Nutrient reference values for Australia and New Zealand, including recommended dietary intakes. Canberra: Commonwealth of Australia; 2006.
7. Brand-Miller J, Foster-Powell K, Colagiuri S, Barclay A. The new glucose revolution. Diabetes and pre-diabetes handbook – the essential diet and lifestyle guide. Sydney: Hachette Australia; 2007.
8. Phillips P, Carapetis M, Stanton C. Fibre facts: dietary fibre. Med Today 2007; 8(2): 63-65.
9. Phillips P, Carapetis M, Stanton C. The glycaemic index explained. Med Today 2006; 7(11): 65-68.
10. Noakes M, Clifton P. The total wellbeing diet. Melbourne: Penguin; 2006.
11. Phillips P, Carapetis M, Stanton C. Sugar and salt: a recipe for problems. Med Today 2007; 8(8): 60-66.
12. National Heart Foundation. Getting patients more active: practical information for general practice. Sydney: NSW Health; 2005.
13. The Royal Australian College of General Practitioners (RACGP). SNAP: A population health guide to behavioural risk factors in general practice. Melbourne: RACGP; 2004.

COMPETING INTERESTS: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.
Ms Carapetis: None.

MedicineToday PEER REVIEWED ARTICLE MedicineToday 2008; 9(10): 43-48

Getting A_{1c} under 7%

The KISS ('keep insulin safe and simple') approach in type 2 diabetes

A_{1c} – or glycosylated haemoglobin – reflects the relation between average blood glucose concentration and diabetic complications.

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

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

Glycaemic control in patients with diabetes is assessed by measurement of blood glucose levels (BGLs) and glycosylated haemoglobin (also known as glycated haemoglobin and HbA_{1c} – shortened to A_{1c}). Measurement of levels of blood glucose gives day-to-day information of the glycaemic highs and lows relating to meals. The A_{1c} value reflects the average daily BGL over about the preceding several weeks.

The recommended target A_{1c} level of below 7% for people with diabetes reflects the trade-off between the benefits and costs of improving glycaemic control – respectively, reduced risk of future diabetic complications and increased risk of hypoglycaemia and weight gain and extra self- and medical care.[1,2] Lifestyle changes and oral hypoglycaemic agents are initially effective in keeping A_{1c} on target in patients with type 2 diabetes. Many patients, however, eventually require insulin therapy for glycaemic control. One approach to controlling blood glucose with insulin is the KISS approach – first control the fasting (i.e. before breakfast) BGL, then the evening BGL and then any mealtime BGL increases.[3-6]

A_{1c} and blood glucose targets

A_{1c}

A_{1c} is the main form of glycosylated haemoglobin and its level reflects the average level of blood glucose over the preceding six weeks or so.

IN SUMMARY

- **A_{1c} – the 'gold standard' for glycaemic control – reflects the relation between average blood glucose over the preceding few weeks and diabetic complications.**
- **In type 2 diabetes, the blood glucose profile can be divided into three components, each of which can be controlled by different strategies:**
  - **fasting glycaemia, controlled by bedtime basal insulin**
  - **daytime blood glucose increment, controlled by morning basal insulin**
  - **prandial increases, controlled by lower glycaemic load meals, increased physical activity, prandial acarbose or bolus insulin.**
- **Controlling preprandial blood glucose levels (BGLs) – i.e. the fasting blood glucose plus any daily basal increment – can result in large decreases in average BGL and A_{1c}. Controlling the size of prandial increments 'finetunes' blood glucose control but will not greatly decrease overall glycaemia if preprandial values are on target.**
- **The KISS approach to controlling blood glucose with insulin involves first controlling the fasting BGL ('First fix the fasting…'), then the BGL before the evening meal ('Then tackle tea…'), then any mealtime BGL increases ('Find the hidden hypers…') and finally looking at glycaemic control over a longer period ('And check the A_{1c}').**

Glycosylated haemoglobin is progressively formed as haemoglobin is exposed to glucose in the plasma. The permanent glycation can occur at different points on the two alpha and two beta amino acid chains that make up the molecule of haemoglobin A, the major form of haemoglobin in adults. The glycosylated form of haemoglobin A is known as HbA_1, and comprises the three subfractions HbA_{1a}, HbA_{1b} and HbA_{1c} (see the box 'Haemoglobin components' on this page). HbA_1 and its subfractions can be measured by various laboratory methods, although generally only A_{1c} is reported.

In the 1990s, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) showed a relation between microvascular complications and levels of glycosylated haemoglobin in people with type 1 and type 2 diabetes, respectively.[7,8] Since then measures of glycosylated haemoglobin have been expressed as a DCCT-equivalent A_{1c} value. Clinicians can use the level of A_{1c} to assess future risks of microvascular complications and the benefits of improving glycaemic control.

Targets for A_{1c} values reflect a balance between the benefits of improving glycaemic control in reducing the risk of future complications, and the costs in terms of increased risk of hypoglycaemia, weight gain and extra self- and medical care. The benefits per unit decrease of A_{1c} are broadly similar in both type 1 and type 2 diabetes (20 to 30% relative risk reduction of diabetic complications per unit [i.e. 1%] decrease in A_{1c}), but the derived risk of hypoglycaemia is much greater (by 40- to 100-fold) in type 1 diabetes.[7,8] Nonetheless, the A_{1c} targets are similar for both type 1 and type 2 diabetes.[1,2]

Generally the A_{1c} target level is below 7% – if this can be achieved without problems. Higher targets, however, may be advisable for some patients, such as the elderly with newly diagnosed diabetes, who are not likely to develop microvascular complications, or those in institutional care, in whom control of symptoms from hyperglycaemia and glycosuria are the priority.

Blood glucose

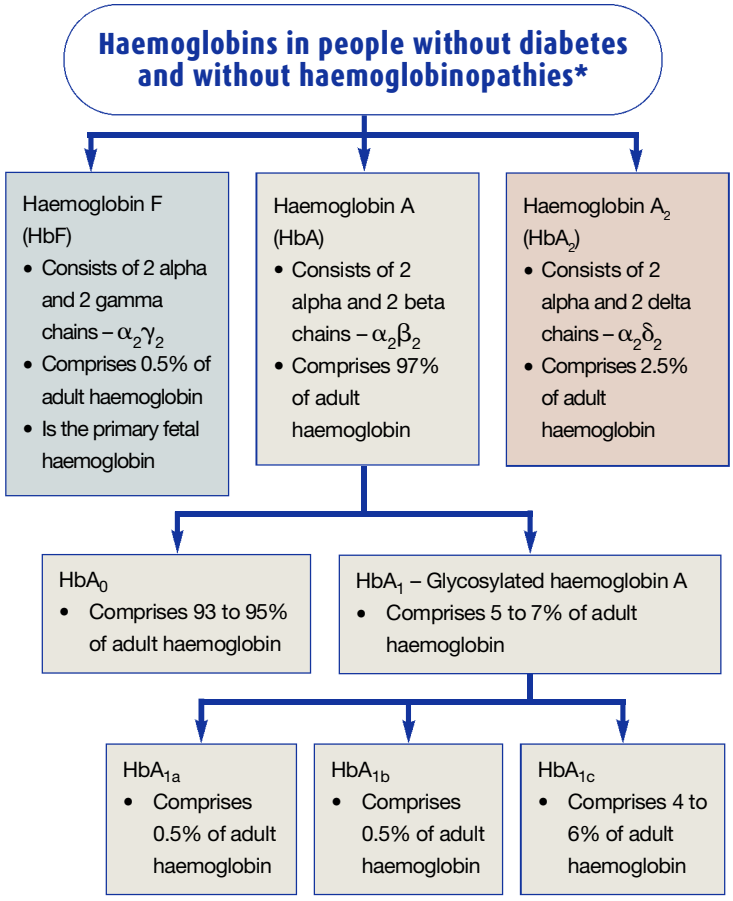
The 24-hour blood glucose profile of a patient with type 2 diabetes can usually be separated into three components (see also Figure 1):[9]

- fasting, which sets the overall basal level of blood glucose
- daytime basal increment, where the blood glucose may increase through the day and decrease through the night
- prandial increment, which is the increase over the preprandial BGL that gives the peak postprandial BGL.

In some patients the basal BGL normally decreases through the day; however, the above general principles still apply. Also, it should be noted that the postprandial BGL is potentially made up of all three components.

The contribution of the three blood glucose components to the average BGL under different circumstances can be calculated. The results

Haemoglobin components



* The proportions of each haemoglobin type differ in people with diabetes or haemoglobinopathies.

The KISS approach to getting A_{1c} under 7%

'First fix the fasting...'

Is bedtime basal insulin needed?

- If the fasting BGL is high, start with 10 units of basal insulin at bedtime. If the fasting BGL is on target but the evening preprandial BGL is high, start with 10 units in the morning.
- Increase doses every two to three days.

'Then tackle tea...'

Is breakfast basal insulin needed?

- If the other (i.e. evening or fasting) preprandial BGL remains high, consider adding a second basal insulin dose.*

'Find the hidden hypers...'

Is breakfast, lunchtime or teatime bolus insulin needed?

- If the BGLs before breakfast and before the evening meal are under control, the BGLs before lunch and before bedtime are usually on target also. If they are not, determine whether the hidden hypers are resulting from breakfast or the evening meal – or both – and review the carbohydrate load of the meal and the physical activity after it and possibly add acarbose with the meal or a bolus insulin (quick-acting or very quick-acting) before.

'And check the A_{1c}'

Is the A_{1c} on target?

- If A_{1c} values, which reflect glycaemic control over several weeks, and BGLs are not both on target, there may be remaining hidden periods of hyperglycaemia or the tests may be giving unreliable results. Review the patient's blood glucose monitoring techniques and also the A_{1c} assay used.

* Publisher's footnote: Please refer to disclaimer on page 27.

Table. Targets for glycaemic control in type 2 diabetes – as recommended by Diabetes Australia and the RACGP[2]

Preprandial blood glucose (mmol/L)	Postprandial blood glucose (mmol/L)	Comment
4 to 6.0	4 to 7.7	Normoglycaemia
6.1 to 6.9	7.8 to 11.0	Minimises macrovascular problems
7.0 and above	11.1 and above	Consider more active treatment Associated with macro- and microvascular complications

Source: Diabetes Management in General Practice 2008/9, published by Diabetes Australia in conjunction with the Royal Australian College of General Practitioners.

broadly agree with the general observation that when average BGL and A_{1c} values are high then the contribution from fasting blood glucose greatly exceeds the prandial contribution. However, prandial increments may be a significant contributor when average BGL and A_{1c} values are closer to target. For example, the prandial increments contribute between 6 and 24% to overall glycaemia when the fasting BGL is 8 mmol/L, but between 11 and 38% when the fasting BGL is 4 mmol/L.

The BGL ranges recommended by the RACGP and Diabetes Australia as targets and indicators of when treatment should be considered in people with diabetes are related to the diabetes diagnostic thresholds of blood glucose – that is, the degree of hyperglycaemia as determined by oral glucose tolerance testing (Table).[2] The aim of treatment is, ideally, normoglycaemia (preprandial BGL, 4 to 6.0 mmol/L; two-hour postprandial BGL, 4 to 7.7 mmol/L), but reducing BGLs to the prediabetes range will improve patient outcomes. Prediabetes BGLs (preprandial, 6.1 to 6.9 mmol/L; two-hour postprandial, 7.8 to 11.0 mmol/L) are associated with an increased risk of macrovascular complications, and BGLs diagnostic of diabetes (preprandial, 7 mmol/L and above; two-hour postprandial, 11.1 mmol/L and above) are associated with both macro- and microvascular complications.

A_{1c} and blood glucose relation

As the A_{1c} level reflects overall glycaemic exposure, theoretically a patient with a constant BGL of 6 mmol/L would have the same A_{1c} value as a patient who spent an equal amount of time with BGL values of 2 and 10 mmol/L. Clearly the first patient's blood glucose profile is preferable to that of the second patient.

There are various equations describing the relation between A_{1c} (in %) and the average BGL over 24 hours (in mmol/L). An easy one to remember is:[10]

Average BGL in mmol/L = $2A_{1c} - 6$

which can be rearranged to read:

A_{1c} = (average BGL in mmol/L + 6) / 2

With this equation, A_{1c} and average BGL have the same numerical value at 6% and 6 mmol/L. At other values, a unit change in A_{1c} is associated with a 2 mmol/L blood glucose change (e.g. 7% and 8 mmol/L; 8% and 10 mmol/L). The same 2 mmol/L blood glucose change per 1% A_{1c} change applies with all the equations.

The recommended glycaemic targets reflect the approximate equivalence of the equation, with ideal BGLs associated with A_{1c} values less than 7% (i.e. BGLs in the 6s) and high BGLs with A_{1c} values greater than 8% (i.e. average BGL greater than 10 mmol/L).

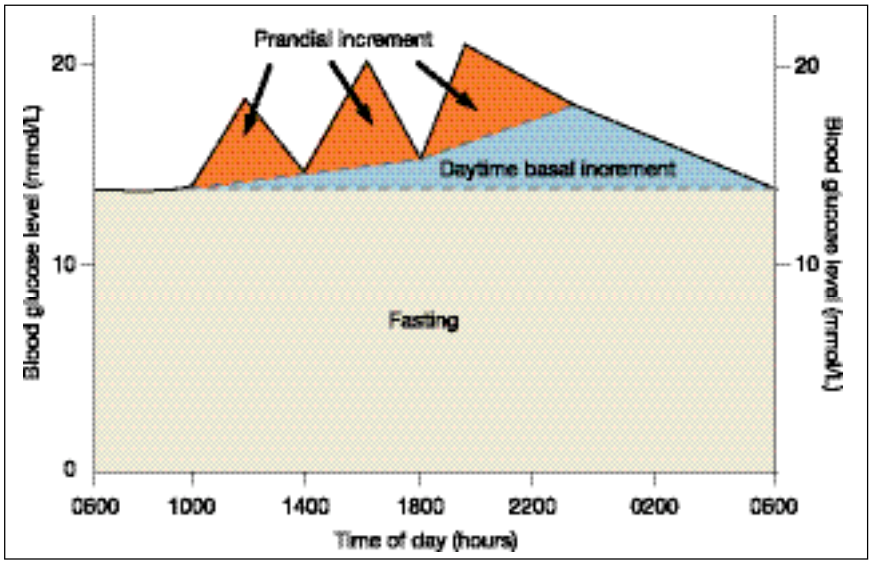


Figure 1. Blood glucose profile in a patient with diabetes (average BGL 16.9 mmol/L), showing the three components of total blood glucose.

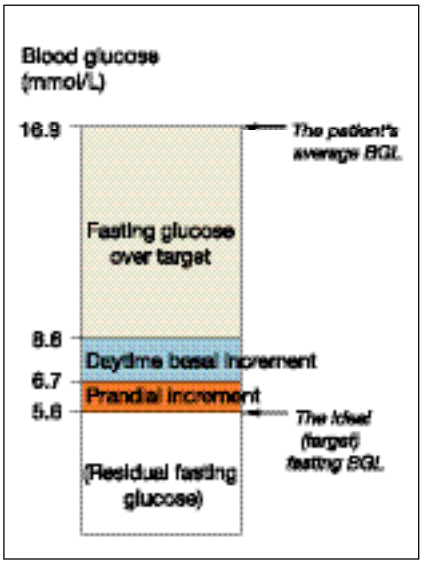


Figure 2. Contributions to glycaemic exposure in the patient in Figure 1 (see text).

The insulin 'KISS'

Lifestyle changes and oral hypoglycaemic changes are initially effective in keeping A_{1c} on target in patients with type 2 diabetes. Many patients, however, eventually require insulin therapy for glycaemic control.

In the 'Keep insulin safe and simple' approach to starting insulin therapy in type 2 diabetes – the insulin 'KISS' – the basal BGLs (fasting or before the evening meal, or both) are the focus because controlling these with basal insulin (i.e intermediate or long-acting insulin) at bedtime and/or breakfast will result in the biggest improvements in glycaemic control.[3-6] Occasionally the prandial increments are important. Glycaemic load and postprandial physical activity may need to be reviewed and/or mealtime acarbose or bolus insulin (quick- or very quick-acting insulin) may be needed. The KISS approach can be summarised by the following jingle (see the box 'The KISS approach' on page 24):

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

In general, lower and slower changes are better when reducing A_{1c} to target – for example, a decrease of 1 to 2 mmol/L in average blood glucose (0.5 to 1% A_{1c}) over three months. Further decreases can be made in subsequent months.

The KISS approach

The KISS approach can be illustrated by considering the case of a patient who has diabetes and the blood glucose profile shown in Figure 1.

'First fix the fasting'

The fasting blood glucose contributes to overall glycaemia for the whole 24-hour period.

In the patient in Figure 1, and as shown in Figure 2, the fasting blood glucose is contributing most to the overall glycaemic exposure. The patient's average BGL over the 24 hours of 16.9 mmol/L is 11.3 mmol/L above the ideal (target) fasting BGL of 5.6 mmol/L. The prandial and daytime basal increments make up 3.0 mmol/L of this amount, and the remaining 8.3 mmol/L is fasting blood glucose. Bringing the fasting BGL (13.9 mmol/L) to target (i.e. to less than 6 mmol/L) by adding a bedtime dose of basal insulin would reduce the average BGL by about 8 mmol/L and also reduce A_{1c} by about 4%.

'Then tackle tea'

Once the fasting BGL is under control, the focus moves to the evening preprandial BGL, which may need to be 'tackled' if it is above target. Adding in a morning dose of basal insulin to bring the evening preprandial BGL back to target could decrease the average BGL by 2 mmol/L.*

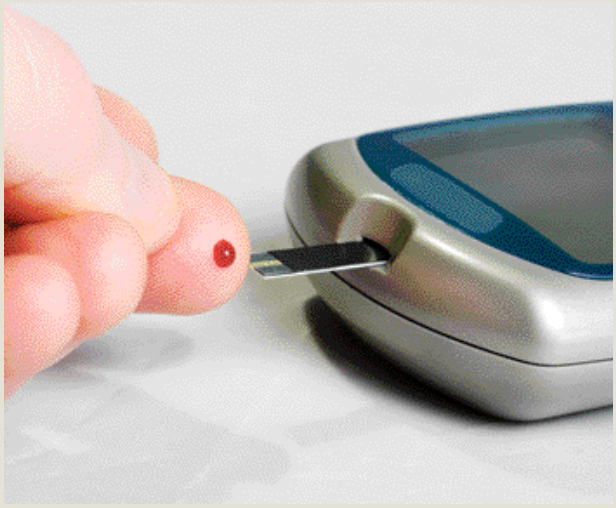
'Find the hidden hypers'

When the BGLs before breakfast and before the evening meal are under control, the other BGLs are usually on target also. However, occasionally BGLs after breakfast (and hence before lunch) and/or after the evening meal (and hence before bedtime) are high because the glycaemic loads of these meals are greater and/or because of inactivity after the meals (such as watching TV, surfing the internet, desk work, driving).

* Publisher's footnote: Please refer to disclaimer on page 27.

Blood glucose monitoring: tips for patients

1. Care for your glucose meter. Clean it often and get it checked regularly by a diabetes nurse. Don't leave it in the sun or the car. Although you can always get another if it 'crashes', they still cost money.
2. Calibrate the meter each time a new bottle or packet of strips is opened and used. Also have quality control checks performed on it regularly. You may still get a reading on your meter if you don't do this, but it may not be accurate and accuracy does matter.
3. Take note of the expiry dates on the strips and quality control fluid. While you don't want to waste any strips, they may not be accurate after the expiry date.
4. Protect the strips from heat and the light. Although they are generally pretty tough these days, keep them in the bottle or foil packets until you use them. Don't leave them in the sun or the car.
5. Wash your hands before you do a test. Having dirty hands may affect the values, and reliability of your results is important.
6. Use a fresh lancet each time – for hygiene reasons and to reduce pain. Never share a lancet with other people. Dispose of used lancets in a sharps container and never in the general rubbish.
7. Always use the recommended amount of blood on a strip, and drip it onto the strip rather than smearing it. Too little may not give a reading and a smear is likely to give an error message.



8. Record all values, not only those that fall within the target. Your doctor or diabetes nurse won't be upset by your 'bad' values – your high and low readings. Do not test only when you know the results will be on or near target in an attempt to keep everyone happy.
9. Check your blood glucose more often if you are unwell.
10. Join the National Diabetes Services Scheme for subsidised strips.

These are the hidden hypers. They are not discrete hyperglycaemic episodes but high levels of blood glucose persisting for longer than expected, possibly because of larger then expected prandial increments or because the blood glucose is not decreasing as quickly as expected. They are 'hidden' because the BGLs being paid attention to first are the morning and evening preprandial BGLs.

In the case in Figure 1, the prandial increments are considerable. Controlling prandial increments to 3.5 mmol/L by changing lifestyle (decreasing glycaemic load and/or increasing physical activity) or adding medication (acarbose [Glucobay] with a meal or a bolus insulin before the meal) could decrease average BGL by 1.1 mmol/L.

It is clear that the big decreases in average BGL and A_{1c} come from controlling preprandial BGL values (i.e. the fasting glucose plus any daily basal increment). Controlling the prandial increments 'fine-tunes' blood glucose control but will not greatly decrease overall glycaemia if preprandial values are on target. If the BGL value before a meal is high, the BGL value after the meal will also be high.

Sometimes people confuse the postprandial blood glucose with the prandial increment itself. The postprandial BGL is the sum of the fasting glucose, the basal daily increment and the prandial increment, and its value compared with the preprandial BGL reflects the size of the prandial increment. The BGL after the evening meal may be high because it reflects the sum of the basal daily increment, the fasting blood glucose and the prandial increment.

A common misconception is that foods with a low glycaemic index (low-GI foods) are 'good' and those with a high GI are 'bad' with regard to postprandial BGLs. Although the GI is a significant factor affecting the glycaemic response to foods (the prandial increment), the postprandial BGL is affected by many other factors as well as this, including:

- preprandial BGL (if the value before the meal is high, the value after the meal will also be high)
- glycaemic load of the food (the amount of carbohydrate in a normal serving of the food multiplied by its GI)
- other components of the meal
- method of food preparation
- amount of physical activity after the meal.[11]

Therefore, eating a large amount of a low-GI food may have more of an effect on postprandial BGL (i.e. be more 'bad') than a small amount of a high-GI food. Considering all these variables, it is not surprising that postprandial BGLs vary considerably within the same individual – for example, if a patient's mean prandial increment was 8 mmol/L, the increment would be expected to be more than 11 mmol/L for 20% of the time and less than 5 mmol/L for 20% of the time.[12]

'And check the A_{1c}'

Checking blood glucose before breakfast, lunch, evening meal and bedtime gives one view of blood glucose control – the ups and downs. Checking the A_{1c} gives another view – overall glycaemic exposure.

The A_{1c} may be higher than expected, suggesting either that some 'hypers' have remained hidden or that the measured BGL values may not be reliable, or both.

Blood glucose monitoring can give misleading results in many ways. For example, there may be a technical problem with the meter, strips or patient technique, or the patient may not be recording all the test results or recording only the 'good' values.[9] Some tips for patients on blood glucose monitoring are listed in the box on page 26.

Sometimes it will be the A_{1c} results that are misleading as a number of medical conditions can lead to falsely high or low A_{1c} levels and some of the assays used are subject to interference. The testing laboratory could advise on this, and may suggest use of a different assay system for A_{1c} determination.

An alternative to the measurement of A_{1c} as a means of monitoring the average glucose level is measurement of fructosamine (also known as glycosylated albumin). The half-life of glycosylated albumin, the major glycosylated protein measured by this assay, is about 19 days (compared with haemoglobin's half-life of about 50 to 55 days). This assay therefore reflects glucose levels over a much shorter time period than A_{1c} measurement. The fructosamine value can be compared with, and therefore used to check, the A_{1c} value in terms of standard deviation above the upper limit of the relevant normal reference range.

Conclusion

While BGL measurement gives day-to-day information on glycaemic status, A_{1c} measurement gives an indication of glycaemic control by assessing average glucose levels over the preceding few weeks, as reflected by the permanent glycation of a small fraction of the haemoglobin molecules in the blood.

Getting basal BGLs (i.e. the fasting BGL and the BGL before the evening meal) on target by the use of basal insulin gives the greatest improvements in glycaemic control in patients with type 2 diabetes requiring insulin. Occasionally postprandial BGLs are important, and then glycaemic load and postprandial activity may need to be reviewed and/or mealtime acarbose or bolus insulin may be needed. MT

References

1. American Diabetes Association. Standards of medical care in diabetes – 2008. Diabetes Care 2008; 31 Suppl 1: S12-S54.
2. Harris P, Mann L, Marshall P, Phillips P, Webster C. Diabetes management in general practice 2008/9. 14th ed. Canberra: Diabetes Australia; 2008. Available online at http://www.racgp.org.au (accessed September 2008).
3. Phillips P. KISS: 'keep insulin safe and simple'. Part 1: initiating insulin in type 2 diabetes. Medicine Today 2007; 8(3): 23-34.
4. Phillips P. KISS: 'keep insulin safe and simple'. Part 2: living with insulin and type 2 diabetes. Medicine Today 2007; 8(4): 43-54.
5. Phillips P. KISS: 'keep insulin safe and simple'. Part 3: troubleshooting insulin problems in type 2 diabetes. Medicine Today 2007; 8(5): 47-55.
6. Phillips P. KISS: 'keep insulin safe and simple'. Part 4: titrating insulin in type 2 diabetes. Medicine Today 2007; 8(6): 43-52.
7. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-986.
8. United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in people with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-853.
9. Hirsch IB, Bergenstal RM, Parkin CG, Wright Jr E, Buse JB. A real-world approach to insulin therapy in primary care practice. Clin Diab 2005; 23: 78-86.
10. Simeon S, Phillipov G, Seaborn CJ, Phillips PJ. Correlation of blood glucose and glycated haemoglobin values. [Abstract.] Australian Diabetes Society, Annual Conference, 1994; E4.
11. Phillips P, Carapetis M, Stanton C. The glycaemic index explained. Medicine Today 2006; 7(11): 65-68.
12. Cooling N, Norton J, Calvert D, Phillips P. Nutritional physiology and pathophysiology: studies of glycaemic response – importance of individual variability. In: Wahlqvist ML, Truswell AS, eds. Recent advances in clinical nutrition II. London: John Libby and Co; 1986; p. 313-315.

COMPETING INTERESTS: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.

MedicineToday PEER REVIEWED ARTICLE

MedicineToday 2008; 9(11): 22-34
Updated February 2008

Insulin analogues

What do they offer to the insulin KISS ('keep insulin safe and simple')?

The genetically engineered basal and bolus insulin analogues have profiles that more closely match pancreatic insulin secretion than the traditional basal and bolus insulins.

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

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

The goal of insulin therapy is to achieve normoglycaemia or as near to it as possible without too much hassle or risk for the patient. Unfortunately the profiles of the traditional intermediate-acting and short-acting insulins and the traditional delivery systems (insulin vials and disposable syringes) are far from ideal, making the achievement of ideal glycaemic control difficult and causing episodes of hypoglycaemia. The newer genetically engineered insulin analogues and the newer insulin delivery systems involving disposable and reusable insulin injectors have considerable advantages over their precursors but are still not perfect. Currently there are five insulin analogues on the market: detemir (Levemir) and glargine (Lantus) are basal insulin analogues, and aspart (NovoRapid), glulisine (Apidra) and lispro (Humalog) are bolus insulin analogues.

This article outlines the limitations of the older insulin preparations and delivery systems and discusses the advantages and limitations of the insulin analogues. It also suggests ways to make best use of the available insulin analogues in type 2 diabetes, following the insulin KISS approach ('keep insulin safe and simple' – i.e. first control the fasting blood glucose level [BGL], then the evening BGL and then any mealtime BGL increases).[1-5]

IN SUMMARY

- **The first insulin analogue – the bolus insulin lispro – became available about 10 years ago.**
- **The basal insulin analogues detemir and glargine have relatively flat and reproducible profiles over 24 hours. Once-daily dosing with these insulins gives more constant and more predictable blood glucose levels than those associated with use of the isophane insulins.**
- **The bolus insulin analogues aspart, glulisine and lispro each have a quicker onset of action, a sharper peak and a shorter duration of action than neutral insulin. They may give better postprandial glycaemic control than neutral insulin, and less hypoglycaemia.**
- **Premix preparations of aspart and lispro are available. However, and at least when starting insulin, better glycaemic control, less weight gain and less hypoglycaemia are generally achieved using bedtime basal insulin and maintaining oral hypoglycaemics than using a premixed insulin.**
- **Insulin injectors are now used by most patients but patients should have syringes available and know how to draw up insulin from the insulin cartridge or prefilled injector in case their injector is broken.**

Insulin therapy

The ideal

Ideally, therapeutic insulin would have a profile closely resembling the levels of insulin in a

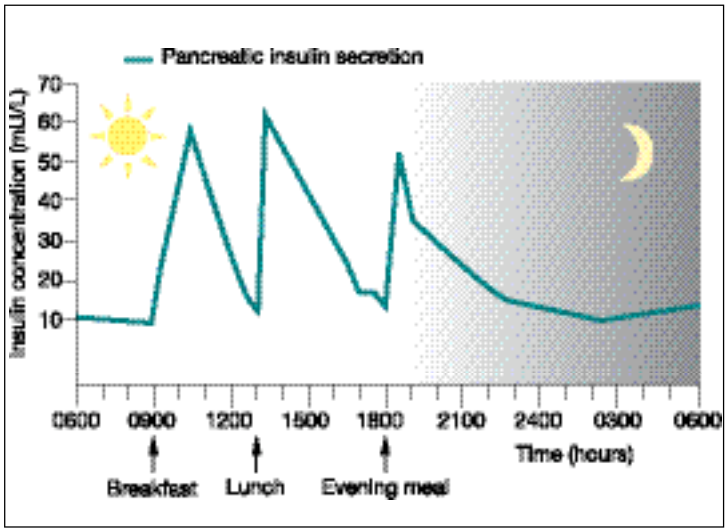


Figure 1. A normal 24-hour profile of insulin secretion.

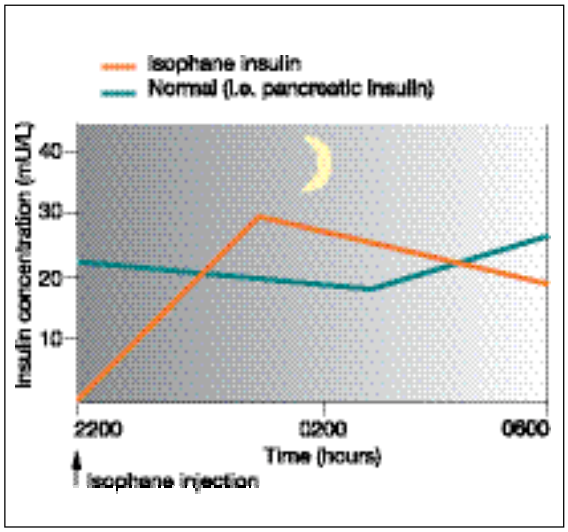


Figure 2. Night-time insulin profiles.

person without diabetes (Figure 1) and would be delivered into the portal circulation, as occurs with pancreatic insulin secretion.

In the ideal therapeutic insulin profile, a basal level of insulin would be maintained throughout the 24 hours. There would be a slight dip in insulin levels at night when many of the body's functions are at their 24-hour low (e.g. blood pressure, temperature and cortisol level all decrease), and a slight rise in the early hours of the morning as the body starts working (and blood pressure, temperature and cortisol level increase). When food is eaten, a bolus of insulin would match the nutrients being absorbed and minimise prandial excursions. Because the liver has a major role in controlling the flux and metabolism of absorbed nutrients, insulin would be delivered at a higher concentration in the portal circulation. Circulating insulin would be rapidly cleared so that insulin levels reflect the natural secretion of insulin in response to delivery of absorbed nutrients.

Available insulins and delivery systems

The currently available therapeutic insulins are the very quick-acting bolus and long-acting basal insulin analogues introduced over the past decade, the older quick-acting neutral insulin (also known as regular insulin and soluble insulin) and intermediate-acting isophane insulin, and biphasic mixtures of some basal and bolus insulins. Insulin preparations are discussed in more detail later in the article.

Most patients now use multidose insulin injectors to deliver insulin, as they are generally more convenient than insulin vials and disposable syringes. Pen injectors can be either disposable devices that are prefilled or reusable devices that can be reloaded using 3 mL cartridges. The disposable injectors are convenient but take up more storage room in the fridge and have a larger carbon footprint because of higher costs of manufacture, storage, transport and disposal. Older patients and those with limited vision or dexterity may prefer to use the larger prefilled disposable device known as InnoLet. This device is easily adjusted, has large numbers that are easy to see, is easy to grasp and has a plunger that is easily depressed. However, it is only available for use with certain insulins. (Details of the available insulins and their delivery devices are provided later in the article in Tables 1 and 3.) All patients using insulin injectors should also have syringes available and know how to draw up insulin from the insulin cartridge or injector in case their injector is broken.

Insulin pumps are an alternative to syringes and insulin injectors but at present are used by only a small proportion of insulin users, although the numbers are increasing. Insulin pumps have the capacity to continuously vary the rates of basal and bolus insulin delivery.

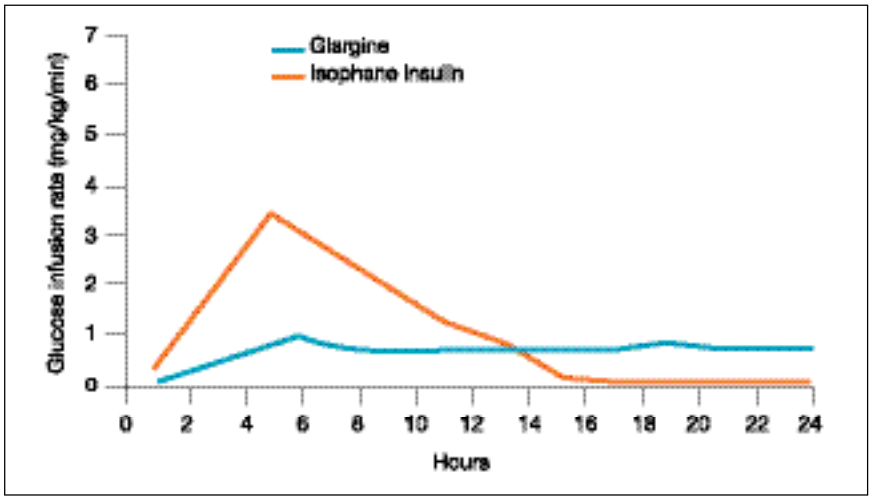


Figure 3. Time–action profiles of glargine and isophane insulin.

Limitations of therapeutic insulins and delivery systems

The current therapeutic insulin preparations and insulin delivery systems have several intrinsic limits, as discussed below.

Insulin delivery is not responsive

Insulin delivery is not responsive to circulating nutrient levels or to nutrient delivery. Although patients can measure the levels of one nutrient (glucose) and learn to assess the effects of current food intake of future nutrient/glucose levels, the measurement and assessment are often inaccurate and imprecise.

Insulin delivery is not on an 'as needed' basis

Insulin doses are deposited subcutaneously on several occasions in the day and are absorbed into the systemic circulation rather than being continuously and variably delivered into the blood of the portal circulation.

Although the rates of basal and bolus insulin delivery can be continuously varied using insulin pumps, dosage adjustments are under the control of the patient and are not reliably responsive to nutrient levels and delivery.

Some experimental systems continuously deliver insulin into the portal circulation but the same limitations apply as for subcutaneous continuous delivery. Also, the systems are difficult to install and maintain and have additional risks, including infection.

Insulin profiles are not ideal, or even close

The traditional intermediate- and short-acting insulin preparations (isophane and neutral insulin, respectively) have profiles that are far from the basal and bolus insulin profiles of a person without diabetes. They have the added disadvantage of considerable variability.

The profile of isophane insulin is far from flat (Figure 2). If this insulin is given at night, levels often peak at the nadir of the body function and then fade as the body systems are awakening. This pattern is the opposite of normal physiology and may lead to hypoglycaemia during the night and hyperglycaemia in the morning. Variability of absorption results in variable effects on the basal insulin profile and unpredictable and variable BGLs.

Similarly the profile of neutral insulin is far from ideal. It lags behind the immediate postprandial rise in blood glucose and lingers despite the later fall in the glucose level. Variability of insulin absorption results in variable insulin levels and in variable and unpredictable postprandial BGLs.

Summarising the limitations

It is therefore no surprise that blood glucose control using traditional insulin delivery systems and insulin preparations is so difficult:

- insulin delivery is systemic rather than portal
- dosage adjustment is intermittent and not continuous
- assessment and anticipation of current and future nutrient levels and fluxes are imperfect
- insulin profiles are inappropriate and variable.

These limitations of insulins and delivery systems apply in both type 1 and type 2 diabetes but particularly in type 1 diabetes where the person is totally dependent on exogenous insulin to control nutrient metabolism (including glucose). The continuing endogenous insulin secretion in type 2 diabetes buffers mismatches between insulin requirements and exogenous insulin delivery and the limitations have much less effect.

The basal insulin analogues

Introducing the basal analogues

Theoretically, multiple injections over 24 hours of neutral insulin, which has a peak of action between two and five hours after injection and a duration of action of six to eight hours, could provide the necessary basal insulin between meals and overnight and bolus insulin at mealtimes. In fact, until the 1930s this is the way insulin was used.

Longer-acting preparations of insulin were developed in the 1930s by adding zinc or protamine (a basal protein extracted from fish sperm) to neutral insulin. The protamine and zinc insulins are insoluble and are absorbed more slowly than neutral insulin. Only the protamine-based longer-acting preparations are available in Australia now, the insulin zinc

Table 1. Basal insulins for use in type 1 and type 2 diabetes

Insulin preparation	Delivery devices			Comments
	Syringe (vials)	Prefilled multidose disposable device	Reusable device (loadable cartridges)	
Basal insulin analogues (long-acting)				
Detemir – Levemir	Not available	Available – FlexPen	Available – Penfill	PBS-subsidised for type 1 diabetes only
Glargine – Lantus	Available	Available – SoloStar	Available	Injection may sting Maximum dose 80 U in one injection PBS-subsidised for type 1 and type 2 diabetes (except vials)
Traditional basal insulins (intermediate-acting)				
Isophane insulin (human)* – Humulin NPH	Available	Not available	Available – HumaPen	–
– Protaphane	Available	Available – NovoLet and InnoLet	Available – Penfill	InnoLet for patients with low vision and/or dexterity

* Bovine isophane insulin (Hypurin Isophane [NPH]) is rarely used nowadays. It is only available as vials for use in syringes.

suspensions having been withdrawn in 2005. In the manufacture of the protamine preparation (which is known as isophane and also as neutral protamine Hagedorn [NPH] after its developer), neutral insulin binds to the protamine and is precipitated as crystals, resulting in a cloudy solution. Once all the interaction sites are associated with insulin ('neutralised'), the absorption profile of further neutral insulin added to isophane is unaffected. Isophane is the basis for all the intermediate-acting and premixed insulins available in Australia.

Using isophane as basal insulin has made life much easier for people living with type 1 diabetes. However, its peaked profile and variability of absorption causes the previously discussed problems associated with a relatively short duration of action and a variable activity profile.

In the past decade, pharmaceutical companies have successfully genetically engineered the insulin molecule and developed the insulin analogues. Of the two currently available long-acting insulin analogues, glargine was marketed first, in the early 2000s, followed by detemir a few years later. Compared with isophane, they have relatively flat and reproducible profiles over 24 hours (Figure 3). They therefore avoid many of the problems associated with isophane. Although both are TGA-approved for use in type 1 and type 2 diabetes, currently glargine is PBS-subsidised for use in both type 1 and type 2, whereas detemir is PBS-subsidised for use in type 1 diabetes only. Both are more expensive than isophane. The available analogue and traditional basal insulins are listed in Table 1.

Glargine and detemir in detail

Glargine has an amino acid substitution in its molecule that makes it soluble at an acid pH and insoluble at the pH of body fluids. Glargine therefore precipitates at the site of injection, and the precipitated crystals then slowly dissolve, releasing the insulin for absorption.

The amino acid sequence of the detemir molecule has been altered by omitting an amino acid and replacing it with a short chain fatty acid. This makes the insulin soluble and also causes it to associate with albumin in the interstitial fluid and bloodstream. This association with albumin slows both the absorption of insulin from the injection site and its transfer from the bloodstream to the interstitial fluid of tissues and then to the insulin receptors of the target cells.

As both basal analogues are soluble in their delivery formulations, the contents of the vials or other delivery devices do not require mixing before use to ensure that reproducible amounts of basal insulin are injected – as is necessary with isophane insulin. Neither basal analogue can be mixed with bolus insulins.

In patients with type 1 diabetes, clinical trials of both basal analogues compared with traditional basal insulins have shown improvement in A_{1c} levels and fewer nocturnal hypoglycaemic episodes.[6,7] In patients with type 2 diabetes, in whom there is still some endogenous insulin secretion to blunt blood glucose swings, these advantages are less clear. In both patients with type 1 diabetes and those

Table 2. Basal insulin analogues – pros and cons

Pros compared with isophane insulin	Cons compared with isophane insulin
• Consistent profile • Often single daily dose • Less hypoglycaemia than with isophane insulin • No mixing or resuspension needed for injection	• Slower response to dose changes than with isophane insulin • May be confused with bolus insulins as both are clear solutions • Cannot be mixed with bolus insulins* • Glargine may sting when injected

* Little data on safety or efficacy available.

with type 2 diabetes, the basal insulin analogues are absorbed over a longer period than isophane and usually only single daily injections of the analogues are needed. The pros and cons of analogue basal insulin compared with traditional basal insulin are summarised in Table 2.

Some trials have suggested that the use of detemir is associated with less weight gain compared with other insulin preparations, and even with some weight loss.[6]

Using basal insulin analogues in type 2 diabetes

The KISS approach to starting insulin in type 2 diabetes first targets the patient's fasting BGL – that is, before breakfast – and then, if necessary, the BGL before the evening meal.[1-5] In some patients, the BGL before the evening meal is targeted first, and then the fasting BGL. The basal insulins target these 'basal' blood glucose values.

The same 'rules' apply when initiating insulin therapy whether analogue or isophane is used as the basal insulin. Start with 10 units of basal insulin, usually at bedtime (to fix a high fasting BGL), and titrate the dose twice weekly to achieve the target fasting BGL (see the box on basal insulin titration on this page).[1,8] In the occasional patient in whom the fasting BGL is on target but the evening preprandial BGL is high, the basal insulin should be given before breakfast.

Delivery systems

Often the particular basal insulin preparation is chosen not because of its absorption profile but because of the desired method of injection and the availability of that method for that particular insulin preparation. The delivery devices available for the analogue and traditional basal insulins are listed in Table 1.

Potential problem – insulin not lasting long enough

Sometimes the basal insulin analogues 'run out' and do not control the blood glucose towards the end of their duration of action.

For example, a bedtime injection of basal insulin analogue may control the fasting BGL but still be associated with a high BGL before the evening meal. In this case, increasing the insulin dose at bedtime would cause morning hypoglycaemia. The problem of morning hypoglycaemia could be solved by shifting the basal insulin injection to the morning but then the basal insulin from the morning injection may 'run out' overnight and result in morning hyperglycaemia. The better solution would be to use two doses of basal insulin analogue – the morning dose to control basal blood glucose before the evening meal and the bedtime dose to control overnight and fasting glycaemia.*

Basal insulin titration[1]*

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

Mean fasting BGL 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 BGL 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 BGL is <3.0 mmol/L in the preceding week.

* Adapted from *Diabetes Care* 2003; 26: 3080-3086.[8]

* Publisher's footnote: Please refer to disclaimer on page 36.

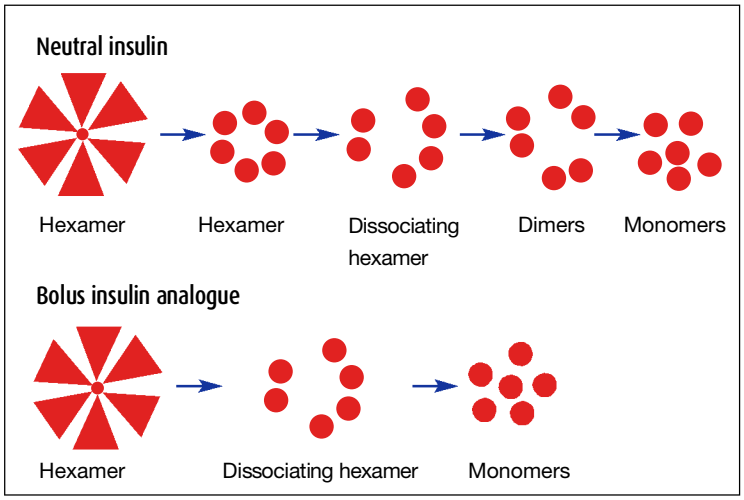


Figure 4. Dissociation of bolus insulins.[9]

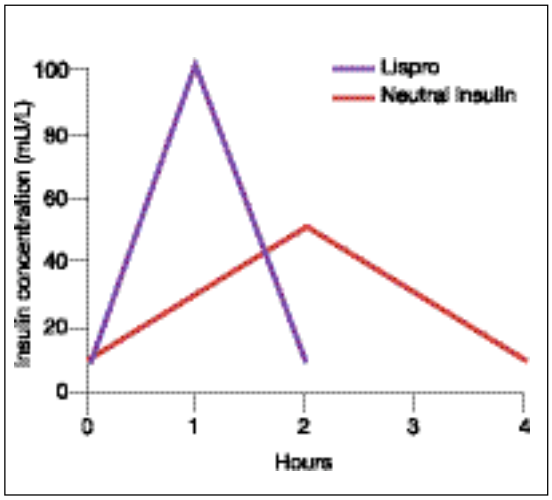


Figure 5. Time–action profiles of lispro and neutral insulin.

Potential problem – insulin lasting too long

On other occasions the opposite occurs. The basal insulin analogue controls the basal blood glucose 12 hours after injection but causes hypoglycaemia towards the end of its duration.

For example, a bedtime injection of basal insulin analogue may not be controlling the fasting BGL but be associated with hypoglycaemia before the evening meal. Shifting the insulin dose to the morning would probably make things worse because the insulin injected in the morning would be likely to be less available overnight, therefore increasing the fasting blood glucose, and more available during the day, therefore worsening hypoglycaemia before the evening meal.

In this situation, the prolonged duration and relatively flat profile of the basal insulin analogues are the problem – these insulins last too long and have too flat a profile. More insulin activity is required during the first 12 hours (in this case during the night) and less in the second 12 hours (in this case during the day). The shorter duration and peaked profile of isophane are advantageous in this situation, and either the addition of a bedtime dose of isophane or a switch to twice-daily isophane would control the fasting blood glucose but not result in hypoglycaemia before the evening meal.

The bolus insulin analogues

Introducing the bolus analogues

The insulin monomers of neutral insulin injected into subcutaneous tissues aggregates into dimers and hexamers, which then gradually dissociate to monomers that are absorbed.[9] Bolus insulin analogues have been genetically engineered to reduce the affinity between insulin monomers and they therefore dissociate and are absorbed more quickly than neutral insulin (Figure 4).

Three analogue bolus insulins are available in Australia: lispro was the first, introduced in the late 1990s, followed by aspart in 2005 and then glulisine in 2007. All three insulins are subsidised by the PBS for use in both type 1 and type 2 diabetes, and they cost only marginally more than neutral insulin. The available analogue and traditional bolus insulins are listed in Table 3.

The profiles of lispro, aspart and glulisine are similar. Compared with neutral insulin, they reach twice the peak in half the time and have half the duration of action (Figure 5).[10]

In clinical trials, the theoretical advantages of bolus analogues over traditional bolus insulin in terms of glycaemic control and hypoglycaemia are less apparent than the advantages of basal analogues in patients with type 1 diabetes.[11,12] There are fewer trials comparing analogue with traditional bolus insulin in type 2 diabetes and less evidence of superiority.

Bolus insulin analogues may have advantages in patients with type 1 diabetes but there are also potential disadvantages (Table 4). The same pros and cons apply to use in patients with type 2 diabetes but, as for the basal analogues, they apply to a lesser degree because the endogenous insulin secretion in patients with type 2 diabetes decreases blood glucose swings compared with those in patients with type 1 diabetes.

Using the bolus insulin analogues in type 2 diabetes

In the KISS approach to starting insulin in type 2 diabetes, usually a single injection of basal insulin and continuation of oral hypoglycaemic agents controls not only the fasting BGL but also BGLs over the 24-hour period.[1-5] As noted earlier, occasionally a second injection of basal insulin is required to control the evening prandial BGL.*

* Publisher's footnote: Please refer to disclaimer on page 36.

continued

Table 3. Bolus insulins for use in type 1 and type 2 diabetes

Insulin preparation	Delivery devices			Comments
	Syringe (vials)	Prefilled multidose disposable device	Reusable device (loadable cartridges)	
Bolus insulin analogues (very quick-acting)				
Aspart – NovoRapid	Available	Available – FlexPen	Available – Penfill	–
Glulisine – Apidra	Available	Available – SoloStar	Not available	Maximum dose 80 U in one injection
Lispro – Humalog	Available	Not available	Available – HumaPen	–
Traditional bolus insulins (quick-acting)				
Neutral insulin (human)*				
– Actrapid	Available	Not available	Available – Penfill	–
– Humulin R	Available	Not available	Available – HumaPen	–

* Bovine neutral insulin (Hypurin Neutral) is rarely used nowadays. It is only available as vials for use in syringes.

Once the fasting BGL has been fixed and the evening preprandial BGL tackled, the next step is to consider stopping or reducing all or some of the oral hypoglycaemic agents. Generally metformin is continued because of its advantages in reducing insulin resistance and helping reduce weight gain, although the daily dose and frequency of dosing may be reduced. As both insulin and glitazone therapy are associated with sodium retention, therapy with pioglitazone (Actos) should be reconsidered (as from October 2008, rosiglitazone has not been subsidised by the PBS for use with insulin). The sulfonylureas may still increase beta cell insulin secretion but could be stopped and then restarted should hyperglycaemia occur that could not be controlled by adjusting the basal insulin. The incretin (specifically glucagon-like peptide-1 or GLP-1) enhancer sitagliptin (Januvia) and mimetic exenatide (Byetta) are not approved for combined use with insulin.

The next step is to consider whether hyperglycaemia is occurring between breakfast and the evening meal or after the evening meal. Finding and fixing these 'hypers' involves reviewing the patient's BGL records and considering lifestyle intervention – reducing mealtime glycaemic load at breakfast or the evening meal or increasing activity after those meals. If lifestyle interventions are not feasible or have not controlled the 'hypers', the options are adding and titrating acarbose (Glucobay) at breakfast and/or the evening meal or adding a bolus insulin before those meals. The theoretical advantage of adding acarbose is a lack of weight gain or hypoglycaemia, both of which may occur with mealtime bolus insulin. The practical disadvantage is the need to start acarbose at a low dose and titrate the dose slowly, and the potential for gastrointestinal side effects (particularly bloating and flatulence). Starting acarbose at 25 mg before the meal and titrating as needed at one- to two-week intervals to a maximum dose of 200 mg minimises the gastrointestinal side effects and may control postprandial glycaemia after breakfast and before lunch and/or after the evening meal.

If postprandial glycaemia is still a problem, as indicated by A_{1c} levels still being high, the final step is to start bolus insulin therapy and titrate the dose to control prandial glycaemia. The recommended safe and simple guide is:[1]

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

Blood glucose monitoring equipment and techniques should also be checked, and patients should be reminded to record all their test results, not just the 'good' values.

Delivery systems

As for basal insulin, choosing the bolus insulin depends on the required insulin profile (very quick-acting or quick-acting) and the preferred injecting device (syringe, disposable injector or reusable injector).

Usually patients prefer to use the same device type for their bolus insulin as they are already using for their basal insulin.

As long as the devices for the two insulin types can be easily differentiated, this is sensible. However, using the same injecting device type increases the chance of the patient giving a wrong dose of insulin – a bolus dose of a basal insulin or vice versa. This mistake is especially likely if analogue basal insulin is used because then both the basal and the bolus insulins are clear solutions – and not differentiated by the cloudiness of the isophane basal insulin.

Sometimes the device type used for the basal insulin is not available for the bolus insulin. In this case the choice is between having two different injectors or changing to a different basal and/or bolus insulin so the same injector type can be used for both. The delivery devices available for the analogue and traditional bolus insulins are listed in Table 3. Unfortunately the InnoLet injecting device is not available for a bolus insulin.

Potential problem – insulin too quick and too peaked

The rapid onset and high peak concentration of the analogue bolus insulins may cause hypoglycaemia if inadequate amounts of carbohydrate are eaten, such as after the classic Australian meal of steak and salad. Ensuring meals have a carbohydrate component – bread, potato, pasta or rice – should avoid such hypoglycaemia.

Potential problem – insulin not lasting long enough

The rapid offset of the analogue bolus insulins may mean that the insulin level before the next meal is inadequate to control basal glycaemia – that is, the insulin 'runs out'. Simply increasing the bolus dose in an attempt to counteract this may cause postprandial hypoglycaemia.

The options in this situation are to have the first meal later or the second meal earlier so the analogue bolus insulin is still working before the second meal, to increase the basal insulin dose or to switch from the analogue bolus insulin to a traditional bolus insulin, which will have a longer duration of action. Probably the simplest and best solution in this case is to use a traditional bolus insulin. Insulin therapy should, in principle, fit the patient's lifestyle, not vice versa, and shifting a meal may affect people other than the patient. Increasing the dose of basal insulin, which has been controlling basal daytime and night-time glycaemia, is likely to cause hypoglycaemia.

Table 4. Bolus insulin analogues – pros and cons

Pros compared with neutral insulin	Cons compared with neutral insulin
• Inject when eating • Less hypoglycaemia than with neutral insulin • Better postprandial glycaemic control than with neutral insulin	• Need to eat promptly after injection • Possible insulin 'run out' before next meal • Need adequate carbohydrate in meal

A word about premixes

Some practitioners hope that 'one size will fit all' and use premixed insulin preparations that contain basal and bolus insulins in fixed proportions. For clothing, one size – extra large – does fit all, although not very comfortably or elegantly. For insulins, however, one size – premixed – often doesn't fit and also causes problems. The quick-acting insulin can cause hypoglycaemia and extra weight gain, and the fixed proportions of short-acting insulin and longer-acting insulin can make titration difficult because changing the dose changes both bolus and basal components at the same time.[13] Generally, and at least when initiating insulin therapy, using a bedtime basal insulin dose and maintaining oral hypoglycaemic agents produces better glycaemic control, less weight gain and less hypoglycaemia than twice daily basal insulin, twice daily premixed insulin or basal/bolus insulin schedules.[13]

The bolus insulin analogues cannot be mixed with the basal insulin analogues. However, aspart and lispro can be mixed with their respective protamine-based longer-acting preparations (aspart protamine suspension and lispro protamine suspension) to form biphasic mixtures (Humalog Mix25, Humalog Mix50, NovoMix 30). These mixes have profiles similar to those of the traditional premixed biphasic insulins (i.e. mixed neutral and isophane insulins) apart from the initial faster onset of action. A premix is not available for glulisine.

Conclusion

The genetically engineered insulin analogues and the insulin delivery systems involving disposable and reusable insulin injectors have considerable advantages over their traditional precursors but are still not perfect. The basal and bolus insulin analogues were developed to match basal pancreatic insulin secretion and pancreatic insulin secretion in response to glycaemia better than the previously available basal and bolus insulins.

The basal analogues detemir and glargine have relatively flat and reproducible profiles over 24 hours compared with the older basal insulin, isophane. Once-daily dosing with these insulins gives more constant and more predictable BGLs than those associated with the use of isophane. Sometimes and in some patients, however, they may not last long enough ('run out') and may not control the blood glucose towards the end of their duration of action. At other times, they may last too long and have

too flat a profile if different insulin activities are required at different times of the day.

The bolus analogues aspart, glulisine and lispro have quicker onset of action, a sharper peak and a shorter duration of action than the older bolus insulin, neutral insulin. They may give better postprandial glycaemic control than neutral insulin, and less hypoglycaemia. However, their rapid onset and offset and high peak concentrations may cause problems of postprandial hypoglycaemia and/or preprandial hyperglycaemia later, relating to their acting too quickly or not lasting long enough, respectively. MT

References

1. Phillips P. KISS: 'keep insulin safe and simple'. Part 1: initiating insulin in type 2 diabetes. Medicine Today 2007; 8(3): 23-34.
2. Phillips P. KISS: 'keep insulin safe and simple'. Part 2: living with insulin and type 2 diabetes. Medicine Today 2007; 8(4): 43-54.
3. Phillips P. KISS: 'keep insulin safe and simple'. Part 3: troubleshooting insulin problems in type 2 diabetes. Medicine Today 2007; 8(5): 47-55.
4. Phillips P. KISS: 'keep insulin safe and simple'. Part 4: titrating insulin in type 2 diabetes. Medicine Today 2007; 8(6): 43-52.
5. Harris P, Mann L, Marshall P, Phillips P, Webster C. Diabetes management in general practice 2008/9. 14th ed. Canberra: Diabetes Australia; 2008. Available online at http://www.racgp.org.au (accessed October 2008).
6. Gerich JE. Insulin glargine: long acting basal insulin analogue for improved metabolic control. Curr Med Res Opin 2004; 20: 31-37.
7. Chapman TM, Perry C. Insulin detemir: a review of its use in the management of type 1 and type 2 diabetes mellitus. Drugs 2004; 64: 2577-2595.
8. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26: 3080-3086.
9. Bakaysa DL, Radziuk J, Havel HA, et al. Physicochemical basis for the rapid time-action of $Lys^{B28}Pro^{B29}$-insulin: dissociation of a protein–ligand complex. Protein Sci 1996; 5: 2521-2531.
10. Owens DR, Zinman B, Bolli GB. Insulins today and beyond. Lancet 2001; 358: 739-746.
11. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database of Systematic Reviews 2004; Issue 4: CD003287.
12. Brunelle BL, Llewelyn J, Anderson JH Jr, et al. Meta-analysis of the effect of insulin lispro on severe hypoglycaemia in patients with type 1 diabetes. Diabetes Care 1998; 21: 1726-1731.
13. Goudswaard AN, Furlong NJ, Rutten GE, Stolk RP, Valk GD. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Cochrane Database Syst Rev 2004; Issue 4: CD003418.

COMPETING INTERESTS: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.

MedicineToday PEER REVIEWED ARTICLE MedicineToday 2009; 10(1): 27-34

The insulin KISS in older people with type 2 diabetes ('keep insulin safe and simple')

With increasing frailty in patients with type 2 diabetes, the goal of glycaemic control becomes the maintaining of a balance between hypoglycaemia and hyperglycaemia rather than the preventing of the long-term complications of the disease.

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

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

Type 2 diabetes becomes progressively more common with age, affecting 15 to 20% of Australians over the age of 60 years[1] (Figure 1), and a higher proportion of those in residential care. As people age, generally their comorbidities and use of medications increase and their physical and mental capacities decrease. The pathophysiology and consequences of type 2 diabetes and the priorities for care are different in elderly people than in younger adults. These factors affect targets for glycaemic control, use of oral hypoglycaemic agents and the timing of starting insulin therapy relative to the course of the diabetes.

Insulin therapy is generally started earlier in elderly people with type 2 diabetes than in younger patients with the disease but follows the basic insulin KISS approach ('keep insulin safe and simple' – that is, first control the fasting blood

IN SUMMARY

- **In the 'young old' – people with a chronological age of over 65 years and a biological age of younger than 75 – tight glycaemic control can still reduce the complications of diabetes. In the 'old old' – people with a chronological age of over 65 years and a biological age of 75 or older – tight glycaemic control offers few long-term advantages and increases the burden of care and may reduce quality of life. The goal of glycaemic control in the 'old old' is to maintain a balance between hypoglycaemia and hyperglycaemia.**
- **The range of oral hypoglycaemic agents is more limited in the elderly and insulin therapy is generally started earlier in the course of type 2 diabetes in elderly people than in younger patients with the disease.**
- **Starting insulin in the 'young old' and 'old old' follows the same KISS ('keep insulin safe and simple') approach as applies to younger people, although in the 'old old' preprandial targets are likely to be higher (such as 5 to 7 mmol/L rather than 4 to 6 mmol/mL) to reduce the risk of hypoglycaemia and/or reduce the burden of care.**
- **The basic insulin KISS approach is to first control the fasting blood glucose level (BGL), then the evening preprandial BGL and then any mealtime BGL increases.**
- **The choice of the insulin formulation is largely determined by the injection device suitable for the patient and/or carer but analogue insulins have advantages over traditional insulins in some circumstances.**
- **Premixed insulin preparations offer the benefit of convenience but are limited by fixed, and sometimes inappropriate, proportions of basal and bolus insulins.**

continued

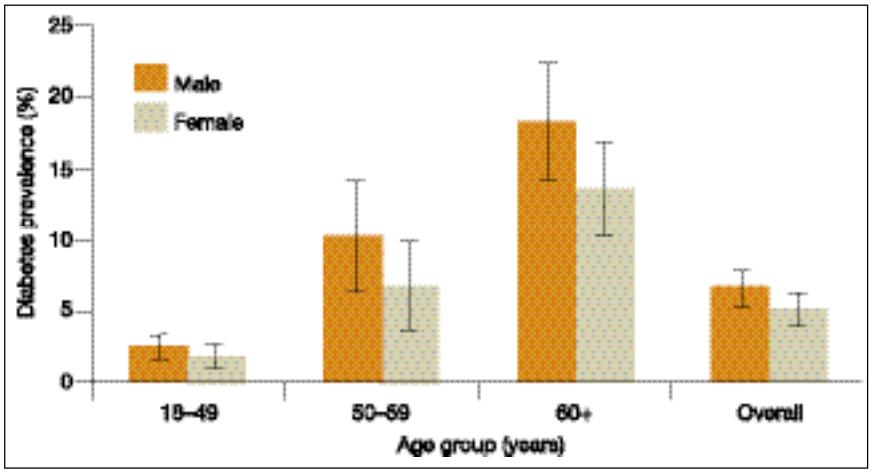


Figure 1. Diabetes prevalence increases with age.[1]

REPRODUCED FROM GRANT J, ET AL. NORTH WEST ADELAIDE HEALTH STUDY. BASELINE BIOMEDICAL AND SELF REPORT DATA. ADELAIDE: POPULATION RESEARCH AND OUTCOMES STUDIES UNIT, SOUTH AUSTRALIAN DEPARTMENT OF HEALTH; MARCH 2005.

glucose level [BGL], then the evening BGL and then any mealtime BGL increases).[2,3]

This article reviews the problems associated with hyperglycaemia in older people with type 2 diabetes and outlines a 'hypoglycaemic hierarchy' to moderate glycaemia and avoid the extremes of hyperglycaemia and hypoglycaemia.

Who is 'old' these days?

As the Australian population ages and the baby boomers move into their 60s, the practical definition of 'old' is becoming biological (or functional) rather than chronological. The default definition of old has generally become the male qualifying age for the age pension, currently 65 years. The elderly have been divided into the 'young old' and 'old old' based on whether they were aged 65 to 75 years or 75 years and older, each group being further subdivided into 'healthy' and 'frail'. This subdivision by chronological age is not particularly useful with regards to assessing care needs as the health and management issues related to many conditions, including diabetes, are generally more dependent on functioning than on age alone.

Taking a biological age of 75 years as the dividing age between 'young old' and 'old old' is likely to be more useful in practice. For example, a biologically young 78-year-old (that is, a person with a chronological age of 78 but a biological age of younger than 75) may still be in full- or part-time work and enjoying a wide range of recreational and social activities whereas a biologically old 78-year-old (that is, a person with a chronological age of 78 but a biological age of 75 or older) may be housebound, or even bedbound, because of previous cardiovascular events, musculoskeletal problems, respiratory disability or other conditions. The medication burden and potential for medication related problems for the biologically 'old' 78-year-old is likely to be much greater than for a biologically younger peer. Similarly, a biologically old 68-year-old (chronological age 68 and biological age over 75) may have many more health issues than a biologically young 68-year-old.

What is known about glycaemic control in older adults?

Not a lot in terms of evidence-based medicine, as there have been no studies specifically in people aged over 75 years. Evidence-based priorities exist for blood pressure control, appropriate use of antiplatelet coagulant agents and foot protection in the elderly,[4] but there are few relevant trials outside these areas. There may be long-term benefits from lipid control for macrovascular disease and from glycaemic control for microvascular disease.

Glycaemic control potentially has considerable short-term and long-term benefits in people with type 2 diabetes.

In the short term, hyperglycaemia can significantly reduce any person's level of energy, alertness and capacity to enjoy life. For older people, fatigue, confusion and daytime sleepiness caused by hyperglycaemia could mistakenly be attributed to the process of getting older or to dementia. In addition to causing annoying polyuria and uncomfortable thrush, glycosuria can cause incontinence and interfere with the activities of daily life and sleep. Hypoglycaemia can change a functional older person into someone who is effectively demented (cognitively impaired) and functionally unable to cope.

In the long term, the macrovascular and microvascular complications of type 2 diabetes may affect quantity and quality of life. Age and type 2 diabetes are two major risk factors for cardiovascular disease and minimising the impact of cardiovascular problems is a high priority in this older population.

For the health care system, congestive heart failure (most commonly due to ischaemic cardiomyopathy) is one of the major reasons for hospital admissions in the western world. For the individual, the effects of myocardial infarction, stroke or lower limb gangrene and need for amputation can be devastating.

The impact of microvascular disease in the short and long term depends on life expectancy, duration of diabetes and the level and progression of existing microvascular disease. Microvascular disease such as severely progressive retinopathy or disabling painful neuropathy can be a major short-term problem. Improving glycaemic control is likely to reduce progression and symptoms. The findings of the United Kingdom Prospective Diabetes Study (UKPDS) suggested that glycaemic control reduced both macrovascular and microvascular complications, but this study was not carried out in an older population.[5] The UKPDS also showed an epidemiological association of benefit from better control.

Setting glycaemic targets

Glycaemic control in patients with diabetes is assessed by measurement of blood glucose levels (BGLs) and glycosylated haemoglobin (also known as glycated haemoglobin and HbA_{1c} – shortened to A_{1c}). Measurement of levels of blood glucose gives day-to-day information of the glycaemic highs and lows relating to meals. The A_{1c} value reflects the average daily BGL over the preceding several weeks.[6]

As previously noted, the evidence base for the older population is less strong than that for younger people and the benefits of long-term glycaemic control are less clear. However, the burdens of the necessary care to produce such glycaemic control are clear, namely insulin dose preparation and administration, extra monitoring of blood glucose, ongoing monitoring of carbohydrate intake, physical activity levels and insulin dosage, and more frequent professional consultations.

It is generally known that:

- the major contributor to overall glycaemia is the fasting blood glucose
- people with type 2 diabetes are not prone to the extreme glycaemic swings that occur in those with type 1 diabetes
- the short-term and long-term problems associated with hyperglycaemia increase progressively with increasing blood glucose and A_{1c} levels.

Worldwide there is a fair consensus about targets for glycaemic control (Table 1). The Australian targets for preprandial BGL of 4 to 6 mmol/L and an overall A_{1c} of below 7% recommended as ideal for people with diabetes are appropriate in some older people.[3] In other older people, however, preprandial BGL targets of 5 to 7 mmol/L and A_{1c} targets of 7 to 9% may be indicated. Such people should aim for preprandial BGLs that are not too low (that is, in the range of 2 to 4 mmol/L) and not too high (that is, in the range of 8 to 10 mmol/L). Glycaemic targets for an individual are a balance between the potential short-term and long-term benefits (symptoms and complications), the burden of this level of care for the person, carer or health care system, and the risks of weight gain and hypoglycaemia associated with tighter glycaemic control.

Table 1. Targets for glycaemic control in type 2 diabetes

	Healthy	RACGP	ADA/EASD	AACE	IDF
A_{1c} (%)	Below 6.0	Below 7	Below 7	6.5 and below	Below 6.5
Fasting blood glucose (mmol/L)	Below 5.5	4 to 6	3.9 to 7.2	6.0 and below	Below 6.0

ABBREVIATIONS: RACGP = Royal Australian College of General Practitioners; ADA/EASD = American Diabetes Association/European Association for the Study of Diabetes; AACE = American Association of Clinical Endocrinologists; IDF = International Diabetes Foundation.

In the absence of evidence-based medicine, the fairytale *Goldilocks and the Three Bears* may offer a guide to glycaemic control – not too high, not too low, 'just right'.

The 'young old'

Case scenario

Alice is 82 years old, lives independently and does all her own housework, shopping and gardening. She enjoys her weekly game of bridge with her friends and regularly goes to the city theatres to see plays (mostly comedies). Her feet swell in summer but she doesn't think she has any other problems with her health. Prediabetes (impaired fasting glucose) was diagnosed three years ago and a recent fasting glucose was 7.6 mmol/L. She has no glycosuria on urinalysis but has had nocturia (one or two voids per night) for the past year or so.

Her weight has been steady at 63 kg, and her height is 1.55 m (BMI, 26 kg/m^2).

Her current medications are simvastatin 40 mg per day, aspirin 150 mg per day and fosinopril/hydrochlorothiazide 10/12.5 mg per day.

- What glycaemic targets would you aim for?
- What special considerations might apply to Alice's glycaemic management now compared with if she was aged 50 years?

Targets

A patient such as Alice who has diabetes and has reached the age of 82 years and remained in good health – a 'young old' person – is likely to have less central obesity and to have avoided the ill effects of cardiovascular disease that were responsible for the earlier mortality of his or her previous peers. He or she will also have less comorbidity than his or her biologically older chronological peers – the 'old old'.

An 82-year-old person with a biological age of, say, a 65-year-old can expect a further 10 to 20 years of living with diabetes, which is plenty of time for diabetic complications to occur and reduce the person's functional independence and quality of life. For such a person, the glycaemic targets may be the same as those of the general population with type 2 diabetes – that is, preprandial BGL below 6 mmol/L and A_{1c} below 7%.

Special considerations

Hypoglycaemic medications

Although the general advantages and disadvantages of hypoglycaemic medications still apply in older patients, there may be some special considerations and changes to the usual hypoglycaemic hierarchy. Even the 'young old' are more likely than younger patients to have medical problems that may affect the use of hypoglycaemic medications.

The more limited range of oral hypoglycaemic options in older patients means that insulin is used earlier rather than later in the course of diabetes. Furthermore, when Alice does start insulin there would be a stronger case for stopping oral hypoglycaemic medications than in younger patients.

Table 2. Medications and renal impairment in type 2 diabetes[7]

Nephrotoxic medications

Radiocontrast agents – the high osmolality ionic contrast agents cause more adverse effects; use the low osmolality nonionic agents instead and avoid dehydration

NSAIDs, including COX-2 'specifics' – use paracetamol instead

ACE inhibitors – check renal function

Medications needing dose adjustment if GFR is below 60 mL/min

Allopurinol – adjust dose to 100 mg per day per 30 mL/min of GFR

Digoxin – check levels

Sulfonamides – halve the dosage if GFR is below 30 mL/min

Medications not to be used if GFR is below 30 mL/min

Some hypoglycaemics – i.e. acarbose, glibenclamide, glimepiride, metformin

Potassium sparing diuretics – i.e. amiloride, triamterene, spironolactone

Tetracyclines

ABBREVIATION: GFR = glomerular filtration rate.

The Cockroft-Gault equation[8]

A simple form of a Cockroft-Gault equation for calculating GFR is:

$$\text{For women, GFR (mL/min)} = \frac{(140 - \text{age}) \times \text{weight}}{\text{serum creatinine } (\mu\text{mol/L})}$$

where weight is 'healthy' weight in kg, calculated by height in cm minus 100.

For men, use the above equation and multiply the answer by 1.25.

In Alice's case (age 82 years, height 155 cm),

- if her serum creatinine were 100 µmol/L then her GFR would be ([140 – 82] x [155 – 100]) ÷ 100 = 32 mL/min.
- if her serum creatinine were 120 µmol/L then her GFR would be ([140 – 82] x [155 – 100]) ÷ 120 = 27 mL/min.

ABBREVIATION: GFR = glomerular filtration rate.

Renal function

Doses of certain medications may need to be adjusted in a person of any age with impaired renal function. If a patient's glomerular filtration rate (GFR) is less than 60 mL/min (but not less than 30 mL/min), then dosage adjustment of some medications is advised. If the GFR is less than 30 mL/min, certain medications should not be used and the dosage of many others should be adjusted (Table 2).[7]

Renal function declines with age and a person's GFR falls roughly 1 mL/min each year, even if the person is healthy. In older people, therefore, a normal serum creatinine (in the range 50 to 110 µmol/L) may be associated with a low GFR. For example, if Alice's serum creatinine were greater than 100 µmol/L, her GFR would be less than 60 mL/min, and if it were greater than 120 µmol/L, her GFR would be less than 30 mL/min, as calculated using the Cockroft–Gault equation, which takes into account her age (see the box on this page).[8] Although metformin is the appropriate initial oral hypoglycaemic medication for both a patient aged 50 years and a 'young old' patient such as Alice if renal function were normal (with dosage increments up to a total dose of 2 to 3 g per day), it should be used at lower doses (such as up to 1 g per day) if GFR were between 30 mL/min and 60 mL/min and not be used at all if GFR were less than 30 mL/min.

It should be noted that estimated GFR (eGFR), which is now calculated (using a different formula to the Cockroft-Gault equation) and reported by most Australian laboratories with every serum creatinine ordered for adult patients, should not be used to estimate GFR to guide drug dosage. For dosage adjustment, the Cockroft-Gault equation should be used.

The choice of sulfonylurea might also be affected by the patient's GFR because both glimepiride and glibenclamide have renally excreted active metabolites that may accumulate and cause hypoglycaemia.

Also, acarbose is contraindicated in patients with severe renal impairment, further limiting the range of available oral hypoglycaemic agents.

Oedema

Alice's leg oedema may be an ongoing problem and could be contributing to her nocturia as the peripheral fluid moves from the extracellular to the plasma compartment and is excreted. If so, use of a glitazone as the hypoglycaemic agent would be expected to worsen this and potentially precipitate cardiac failure because of the side effect of fluid retention.

When insulin is started, Alice should be warned that her leg swelling might get worse because insulin increases renal sodium retention. She may need to consider wearing a support stocking.

Hypoglycaemia

Many people think all those using insulin are in the same category. However, the pathophysiology of type 1 and type 2 diabetes are very different, as is the likelihood of glycaemic swings. The rate of hypoglycaemia is much lower in type 2 than type 1 diabetes. In the two trials assessing the relation between glycaemia and complications, Diabetic Control and Complications Trial (DDCT) and UKPDS, 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.[5,9]

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.

Personal, medical, medication-related and diabetes management factors increase the risk of hypoglycaemia (Table 3). These factors increase the hypoglycaemic effect of insulin, reduce the effectiveness of counter-regulation or delay recognition of hypoglycaemia.

Because of their age, older people are more likely to have social and medical problems and to be taking potentially dangerous medications. As people with diabetes age they develop 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.

Hypoglycaemia is therefore more likely to occur in older people because they are more likely to have hypoglycaemic risk factors. It is also more likely to have catastrophic effects, including myocardial infarction, stroke, seizure or trauma caused by falling.

In older patients with hypoglycaemic risk factors or a history of severe hypoglycaemia, the following items 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.

Initiating insulin in the 'young old'

Starting insulin in the 'young old' follows the same KISS approach as applies to younger people, although preprandial BGL targets may be slightly higher to reduce the risk of hypoglycaemia and/or the burden of care.[2]

The 'old old'

Case scenario

Allan is 72 years old and a nursing home resident. A myocardial infarction followed by atrial fibrillation and a large embolic stroke two years ago left him with a dense right hemiplegia and he is unable to live independently. He is able to sit out of bed but is not able to communicate well and does not seem interested in reading, watching television or listening to music or the radio.

He has type 2 diabetes and his current hypoglycaemic medication is intermediate-acting basal insulin (isophane) 24 units in the evening and metformin 500 mg twice daily.

The nursing staff are concerned about his blood glucose values: his fasting (morning preprandial) BGL is 8 to 10 mmol/L, and his other random BGLs through the day range widely between 6 and HI (that is, over 25 mmol/L).

- How would you decide whether to intensify insulin treatment?
- Assuming you are going to intensify insulin treatment, what would be your next steps?
- Should you use analogue insulins?
- Should you use a premixed insulin preparation?

When to intensify insulin therapy

In the 'old old' there may not be any long-term theoretical benefits of tight glycaemic control on diabetic complications. Moreover, ideal glycaemic control (preprandial BGL, below 6 mmol/L; postprandial BGL, below 8 mmol/L) exposes these biologically old people to the risk of hypoglycaemia, which can have severe consequences. The more appropriate preprandial BGL targets for the 'old old' are 5 to 7 mmol/L.

In Allan's case, the goal is to avoid symptoms of hyperglycaemia (confusion and tiredness, which are usually worse after meals) and glycosuria (which can be a special problem in a marginally continent patient, if nocturia becomes frequent or if associated with thrush), without causing hypoglycaemia between meals (with the symptom of confusion).

Allan's fasting BGL of 8 to 10 mmol/L on its own might not prompt action but high preprandial BGLs are likely to be associated with even higher postprandial BGLs, which may cause confusion, tiredness, polyuria or thrush.

Steps in intensifying insulin therapy

Sometimes blood glucose is monitored at times convenient to the nursing staff rather than preprandially. These random blood glucose values are of little use in guiding therapy. The first step in intensifying a patient's insulin therapy would be to check BGLs before the midday and

Table 3. 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)

continued

Basal insulin titration in the elderly

Start with 10 units of basal insulin, either isophane insulin or an analogue insulin, usually at bedtime but for some patients in the morning. Using the guidelines below, adjust the dose twice weekly to reach the target fasting blood glucose level (BGL) of below 6 mmol/L for the 'young old' and below 7 mmol/L for the 'old old'. (The 'young old' are those people with a chronological age of over 65 years and a biological, or functional, age of younger than 75 years; the 'old old' are those with a chronological age of over 65 years and a biological age of 75 years or older.)

Mean fasting glucose over preceding two days (mmol/L)	Insulin increase (U/day)
For a target fasting BGL of below 6 mmol/L:	
Above 10	8
8 to 10.0	6
7 to 7.9	4
6 to 6.9	2
For a target fasting BGL of below 7 mmol/L:	
Above 11	8
9 to 11.0	6
8 to 8.9	4
7 to 7.9	2

- No increase in the insulin dose if the fasting BGL is below 4 mmol/L for the 'young old' or below 5 mmol/L for the 'old old' at any time in the preceding week.
- No increase and small decreases (2 to 4 units) in insulin dose if there is severe hypoglycaemia (requiring assistance) or the BGL is below 3.0 mmol/L in the preceding week.

Adapted from *Diabetes Care* 2003; 26: 3080-3086.[10]

evening meals. If the fasting BGL is above target (for example, above 7 mmol/L) and the other preprandial values are similar to the fasting, increasing the evening intermediate-acting insulin dose is likely to 'fix the fasting' and the other preprandial values are likely to decrease as well. On the other hand, if the fasting BGL is on target (for example, 5 to 7 mmol/L) and the other preprandial BGLs are significantly higher than the fasting (that is, greater than 7 mmol/L) then a second dose of intermediate-acting insulin may be required in the morning. Allan's fasting BGL is 8 to 10 mmol/L, so an increased evening dose of intermediate insulin would be indicated.

As noted, blood glucose target values are likely to be higher in the 'old old'. The usual insulin titration algorithm can be modified accordingly, as shown in the box on this page.[2,10]

Once the preprandial BGL targets are met in an 'old old' patient, it may be appropriate to stop the metformin to reduce the medication burden and check preprandial values two to three times per week at different times of the day.

It should be remembered that intermediate-acting insulin has a peak in its time–action profile about three to five hours after administration that can cause hypoglycaemia in the middle of the day or night, depending on whether it is given in the morning or the evening. If Allan starts becoming confused during the night, it may be due to hypoglycaemia from his evening dose of insulin; checking his BGL in the middle of the night, such as at 2 a.m., would pick this up. Similarly, checking the BGL before lunch will pick up daytime hypoglycaemia after a morning dose of intermediate-acting insulin.

A preprandial BGL of 5 to 7 mmol/L is likely to be associated with a postprandial BGL of around 10 to 15 mmol/L and an A_{1c} of around 7% (see the box on page 43).[11] Once Allan's preprandial values have been on target for several weeks, a measured A_{1c} significantly higher than 8% would suggest postprandial hyperglycaemia and prompt review of the amount and type of carbohydrate being eaten and consideration of adding acarbose (Glucobay) at the preceding meal.

If A_{1c} remains high, it may be necessary to add a bolus insulin, although such use should be minimised because of the risk and danger of hypoglycaemia. The temptation to fix a high preprandial BGL with bolus insulin should be resisted; adjust the preceding intermediate-acting basal insulin dose and/or timing instead.

Bolus insulin may be appropriate in two situations:[6]

- if BGLs before lunch are high despite BGLs before breakfast and the evening meal being on target, the food eaten at breakfast and during the morning being appropriate and a breakfast dose of acarbose being contraindicated or not effective. Increasing the morning intermediate-acting insulin dose is likely to cause hypoglycaemia in the afternoon; adding a dose of quick- or very quick-acting insulin before or with breakfast should control values before lunch
- if BGLs before the evening meal are high despite BGLs before breakfast and lunch being on target, the food eaten at lunch and in the afternoon being appropriate, and a lunchtime dose of acarbose being contraindicated or not effective. Increasing the morning intermediate-acting insulin dose is likely to cause hypoglycaemia before lunch; adding a dose of quick-

BGL and A_{1c} approximations[11]

Average blood glucose level (BGL; in mmol/L) is approximately equivalent to preprandial BGL + 2, and
Average BGL (in mmol/L) is approximately equivalent to (2 A_{1c} – 6)

Therefore, A_{1c} = (average BGL + 6) ÷ 2 and A_{1c} = (preprandial BGL + 8) ÷ 2

In Allan's case, if his average preprandial BGL is 6 mmol/L then his expected A_{1c} would be (6 + 8) ÷ 2 = 7.0%

A website converter of estimated average glucose to/from A_{1c} can be found at: http://professional.diabetes.org/glucosecalculator.aspx

or very quick-acting insulin before or with lunch will control blood glucose before the evening meal.

When bolus insulin is used, 'go low and go slow' – for example, start with 4 units and increase by increments of 2 units.

Once the desired glycaemic control has been achieved, establish a monitoring schedule to avoid hypoglycaemia and hyperglycaemia. Testing preprandial BGLs several times a week will pick up the lows (BGLs of 2, 3 and 4) and the highs (BGLs of 8, 9 and 10) and prompt changes in the basal insulin dose. Measuring the A_{1c} two to three times a year will check the overall long-term glycaemic control and may prompt changes to the glycaemic targets and/or the monitoring schedule.

Choosing the insulin to use

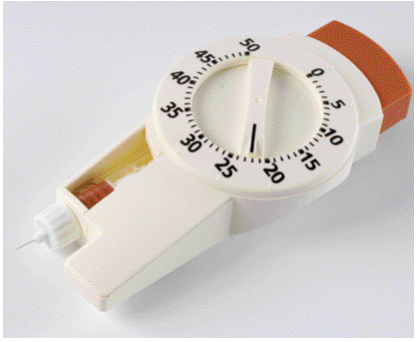
Often the most important factor in choosing the formulation of insulin to use is the injection device available.[12] Most patients now use multidose insulin injectors to deliver insulin, as they are generally more convenient than insulin vials and disposable syringes. Pen injectors can be either disposable devices that are prefilled or reusable devices that can be reloaded using 3 mL cartridges. Older patients and those with limited vision or dexterity may prefer to use the larger prefilled disposable device known as InnoLet, which is easily adjusted, has large numbers that are easy to see, is easy to grasp and has a plunger that is easily depressed (Figure 2).

The delivery devices available for the basal and bolus insulins are listed in Table 4. It should be noted that, with the exceptions of detemir (Levemir) and the vial preparation of glargine (Lantus), the insulin preparations in this table are currently PBS-subsidised for use in both type 1 and type 2 diabetes. Detemir is currently PBS-subsidised for use in type 1 diabetes only.

Insulin analogues

Analogue basal insulins are clear solutions and unlike the cloudy isophane insulin preparations do not require mixing before use to ensure a uniform suspension. This can be a considerable advantage because although the isophane insulins are cheaper for the health care system, they are not always thoroughly mixed by patients or nursing staff. Another advantage of the basal analogues is their long duration and flat profile of activity, which means that the insulin can often be given once daily at any time of the day, as long as that timing is fairly consistent from day to day.

Regular (neutral) and analogue bolus insulins are both clear solutions and do not require mixing. The bolus analogues have the advantage of reaching a peak earlier and controlling postprandial blood glucose better than neutral insulin. Also, they are effective if given immediately before, during or after the meal. Theoretically this could be useful for patients whose food intake is variable, as the dose of bolus analogue could be based on the amount of carbohydrate eaten. However, this complicates the schedule considerably and an alternative strategy might be to stop giving the bolus insulin in this situation. Because of their more rapid onset of action, the bolus analogues also have the potential disadvantage of causing more severe postprandial hypoglycaemia if adequate carbohydrate is not eaten at the meal.



PHOTOLIBRARY

Figure 2. The InnoLet insulin delivery device has a large plunger and a large dial. It is particularly suited to older patients and those with limited vision and dexterity.

Premixed insulins

Premixed insulin preparations are convenient combinations of basal and bolus insulins and are commonly used worldwide. Mixes include bolus/basal proportions of 25/75, 30/70 and 50/50. Preparations are either mixes of quick-acting neutral insulin and intermediate-acting isophane insulin (Humulin 30/70, Mixtard 30/70 and 50/50) or mixes of the bolus analogues aspart and lispro with their respective protamine-based longer-acting preparations (Humalog Mix25, Humalog Mix50, NovoMix 30).

Occasionally premixes match the person's need for basal and bolus insulin but often the fixed combination provides too much bolus for the required basal insulin, or vice versa, and results in problems of hypoglycaemia and/or hyperglycaemia and/or weight gain that are not easy to control. If bolus insulin is required and the proportion of bolus to basal insulin is close to that in a premix and is not expected to change in the future, premixed insulins can simplify the insulin schedule. However, insulin requirements usually do change, and a premix appropriate today may no longer be appropriate in a year's time.

If premixes are used, it is important to be aware of the different effects of the basal and bolus insulins on the blood glucose profile. When increasing or decreasing the dose of the premix because of a problem of excess or inadequate basal or bolus insulin, it is easy to also be causing further

continued

Table 4. Insulins and their delivery devices

Basal insulin

Basal insulin analogues

- Loadable pens – detemir (Levemir), glargine (Lantus)
- Prefilled multidose disposable pens – detemir, glargine
- Vials for syringes – glargine

Isophane insulin

- Loadable pens – Humulin NPH, Protaphane
- Prefilled multidose disposable pens – Protaphane (Novolet and the larger device, InnoLet)
- Vials for syringes – Humulin NPH, Protaphane

Bolus insulin

Neutral insulin, human

- Loadable pens – Actrapid, Humulin R
- Vials for syringes – Actrapid, Humulin R

Bolus insulin analogues

- Loadable pens – aspart (NovoRapid), lispro (Humalog)
- Prefilled multidose disposable pens – aspart, glulisine (Apidra)
- Vials for syringes – aspart, glulisine, lispro

glycaemic problems, which in turn require further adjustments and may cause further problems.

Conclusion

In the 'young old' – a person with a chronological age of over 65 years and a biological age of younger than 75 – tight glycaemic control can still reduce the complications of diabetes. However, in the 'old old' – a person with a chronological age of over 65 years and a biological age of 75 or older – tight glycaemic control offers few long-term advantages and also increases the burden of care and may reduce quality of life. The goal of glycaemic control in the 'old old' is to maintain a balance between hypoglycaemia and hyperglycaemia.

Starting insulin in the 'young old' and 'old old' follows the same KISS ('keep insulin safe and simple') approach as applies to younger people, although in the 'old old' preprandial targets may be higher (such as 5 to 7 mmol/L rather than 4 to 6 mmol/mL) to reduce the risk of hypoglycaemia and/or the burden of care.

The basic KISS principles of insulin therapy – the insulin KISS – are to start basal insulin at 10 units in the evening to control overnight and basal blood glucose, and then add a second basal dose in the morning as needed.* Occasionally daytime hyperglycaemia will be the dominant feature, and the first basal dose is then given in the morning, and the second dose is added if needed in the evening. Hyperglycaemia occurring in the middle of the day (before lunch) or after the evening meal requires review of lifestyle, consideration of acarbose and/or addition of bolus insulin.

Although the choice of the insulin formulation is largely determined by the injection device suitable for the patient and/or carer, analogue insulins have advantages over traditional insulins in some circumstances. Premixed insulin preparations offer the benefit of convenience but are limited by fixed, and sometimes inappropriate, proportions of basal and bolus insulins. MT

* Publisher's footnote: Please refer to disclaimer on this page.

References

1. Grant J, Chittleborough C, Dalgrandy E, Taylor A. North West Adelaide Health Study. Baseline biomedical and self report data. Adelaide: Population Research and Outcomes Studies Unit, South Australian Department of Health; March 2005.
2. Phillips P. KISS: 'keep insulin safe and simple'. Part 1: initiating insulin in type 2 diabetes. Medicine Today 2007; 8(3): 23-34.
3. Harris P, Mann L, Marshall P, Phillips P, Webster C. Diabetes management in general practice 2008/9. 14th ed. Canberra: Diabetes Australia; 2008. Available online at http://www.racgp.org.au (accessed January 2009).
4. Sinclair AJ. Issues in the initial management of type 2 diabetes. In: Sinclair AJ, Finucane P, eds. Diabetes in old age. 2nd ed. Chichester, UK: John Wiley and Sons; 2001.
5. United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in people with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-853.
6. Phillips P. Getting A_{1c} under 7%. The KISS ('keep insulin safe and simple') approach in type 2 diabetes. Medicine Today 2008; 9(10): 43-48.
7. Yong TY, Phillips PJ, Coates PTH. Neglected nephropathy. Aust Fam Physician 2006; 35: 398-402.
8. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.
9. Diabetes Control and Complications Trial (DCCT). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-986.
10. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26: 3080-3086.
11. Simeon S, Phillipov G, Seaborn CJ, Phillips PJ. Correlation of blood glucose and glycated haemoglobin values. [Abstract.] Australian Diabetes Society, Annual Conference, 1994; E4.
12. Phillips P. Insulin analogues. What do they offer to the insulin KISS ('keep insulin safe and simple')? Medicine Today 2008; 9(11): 22-34.

COMPETING INTERESTS: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.