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]

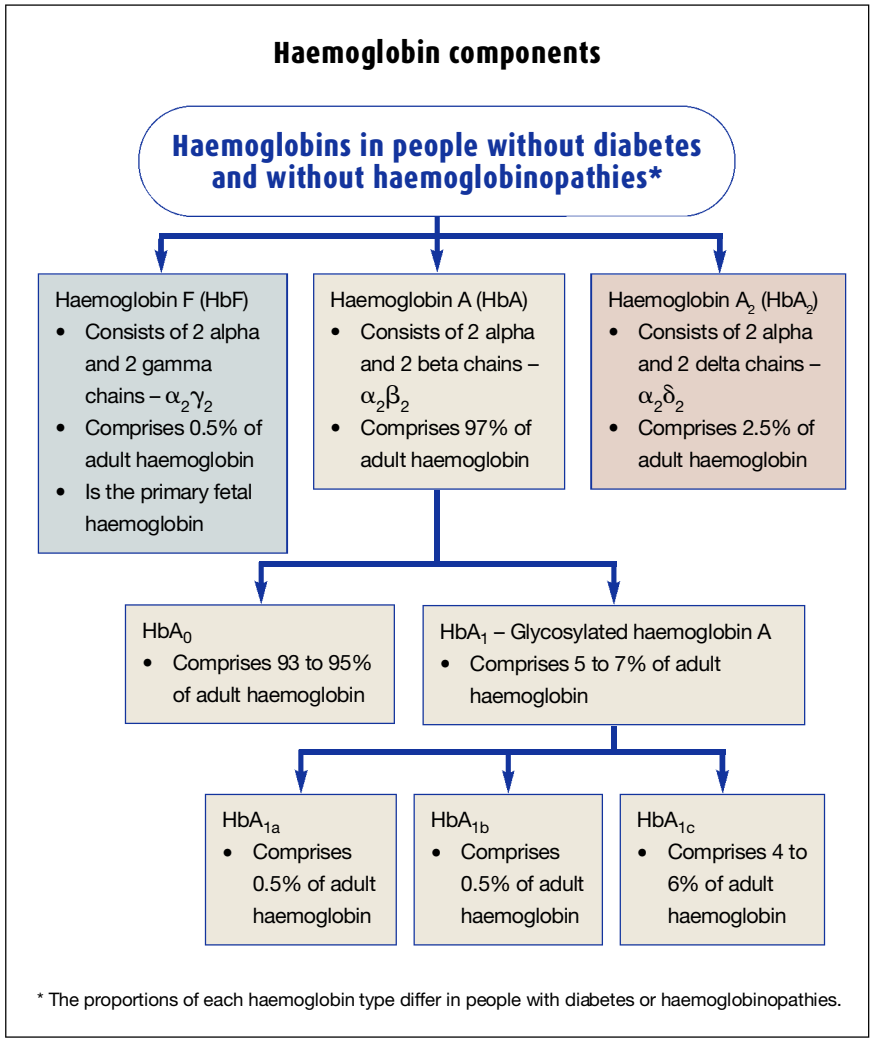
A_{1c} and blood glucose targets

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 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

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.

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).

The insulin 'KISS'

Lifestyle changes and oral hypoglycaemic changes are initially effective in keeping A_{1c} on target in patients with

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.

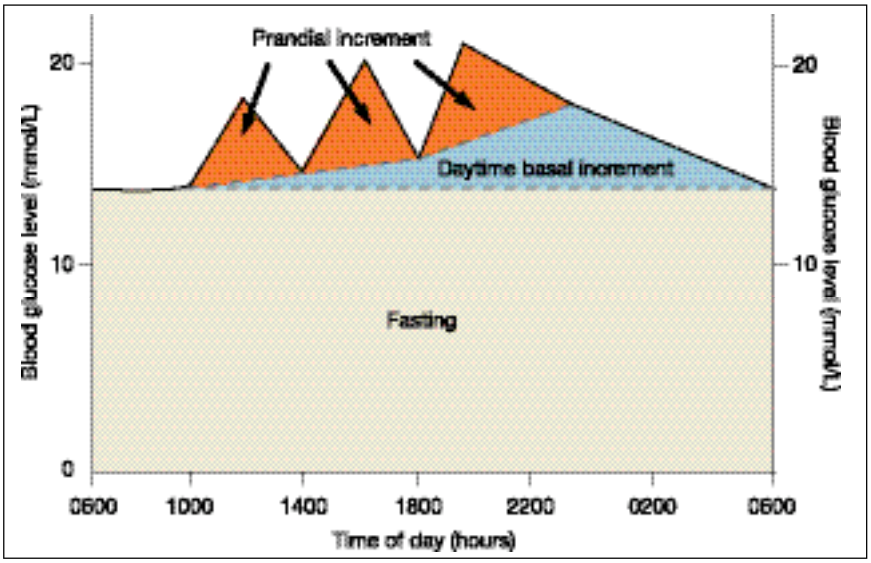


Figure 1. Blood glucose profile in a patient with diabetes (average BGL 16.9 mmol/L), showing the three components of total blood glucose.

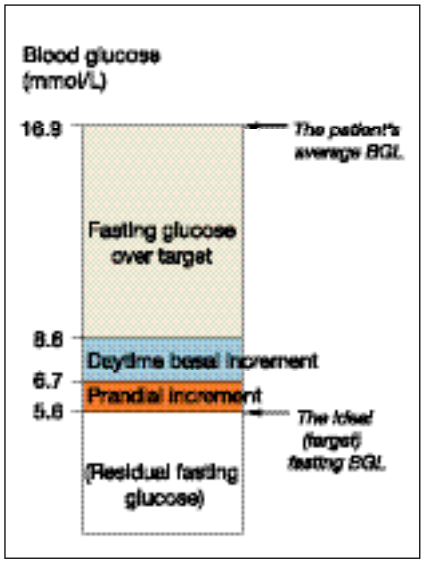


Figure 2. Contributions to glycaemic exposure in the patient in Figure 1 (see text).

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 45):

'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.

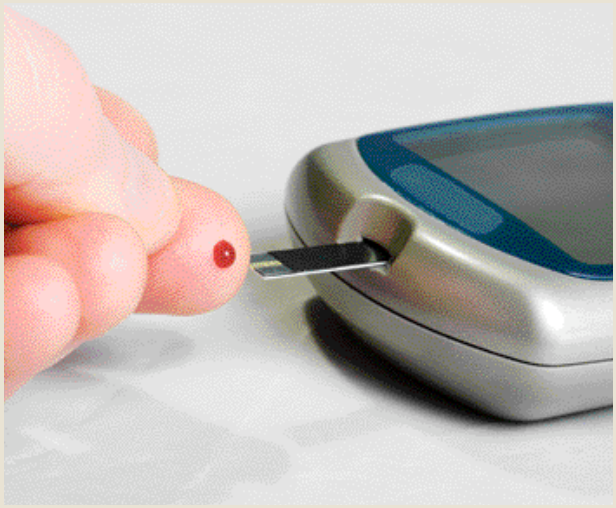
'Find the hidden hypers'

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).

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

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.

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 47.

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.