KISS: 'keep insulin safe and simple'

Part 4: titrating insulin in type 2 diabetes

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

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

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

Initiating insulin therapy

Case scenario

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

IN SUMMARY

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

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PHOTOLIBRARY

both between 6 and 9 mmol/L, and her A_{1c} is 8.0%.

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

What basal insulin schedule do you recommend?

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

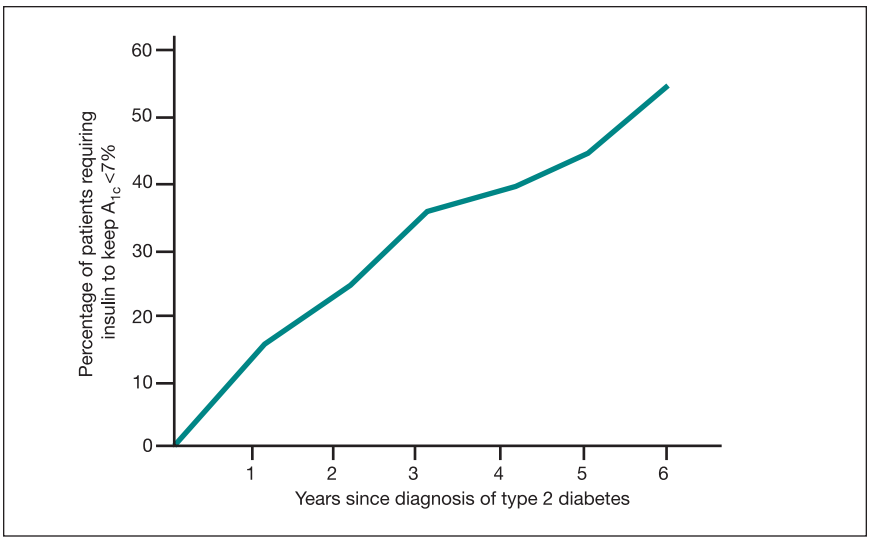

Figure. About 50% of patients with type 2 diabetes will require insulin within six years of diagnosis.[1]

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

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

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

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

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

- when blood glucose is well above target, increase insulin doses by larger amounts than when blood glucose is close to target
- adjust doses every two to three days;

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even better, encourage the patient to change the dose following an agreed protocol, perhaps with advice from the practice nurse.

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

Intermediate acting isophane insulin (Humulin NPH, Protaphane) and the long acting analogue insulins glargine (Lantus) and detemir (Levemir) each have their pros and cons. The choice of which to use is often decided by the patient's choice of injection device – syringe, pen injector or, for those with limited vision or manual dexterity, the larger InnoLet (Table 1).[3] Analogue basal insulins have the advantages over isophane insulin of a more consistent profile, single rather than twice daily dosing and less risk of hypoglycaemia and not requiring mixing or resuspension before injection. There is, however, a slower response to dose changes with analogue basal insulin than with isophane insulin, and basal analogues may be confused with bolus insulins as both are clear solutions. Also, the analogue basal and bolus insulins cannot be mixed with bolus insulins, a flat insulin profile may not suit all patients, and glargine may sting when injected. Currently (May 2007), isophane insulin and glargine are subsidised by the PBS for all insulin schedules; detemir is approved only for use for basal–bolus schedules.

Larger insulin doses and multiple oral hypoglycaemics

Case scenario

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

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

How would you respond?

Insulin dose

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

- starting insulin
- the large insulin doses required.

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

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

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

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

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

The practical implications of larger insulin doses include:

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

Table 1. Basal insulins

Insulin type	Trade name	Delivery device types
Intermediate acting (12 to 24 hours)		
Isophane	Humulin NPH	Syringe Reusable insulin pen
	Protaphane	Syringe Reusable insulin pen Disposable insulin pen A large disposable injection device (InnoLet)
Long acting (24 to 36 hours) – the analogue basal insulins		
Detemir	Levemir	Disposable insulin pen
Glargine	Lantus	Syringe Reusable insulin pen

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Oral hypoglycaemic agents

Metformin has three advantages in patients with type 2 diabetes:

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

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

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

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

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

Morning but not evening BGL on target

Case scenario

Two years later, Mary's A_{1c} is 7.8% and her hypoglycaemic schedule includes metformin 500 mg twice daily and 96 units of basal insulin at bedtime. Her blood glucose profile shows:

- breakfast, 4 to 7 mmol/L
- lunch, 7 to 11 mmol/L
- evening meal, 6 to 9 mmol/L.

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How would you optimise glycaemic control?

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

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

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

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

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

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

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

Isophane insulin has a peak of activity that might occur between breakfast and lunch, depending on the times of the meals. Such a peak might cause low blood glucose values before lunch and, as insulin levels decline after the peak, blood glucose might rise before the evening meal. The simplest solution would be to use an analogue basal insulin, which has a flatter profile than intermediate acting insulin, on either a twice daily or once daily schedule as this might provide sufficient basal insulin to control both fasting and evening glycaemia. Points to consider when switching from isophane insulin to analogue basal insulin are discussed in the box on page 50.

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

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

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Switching from isophane insulin to analogue basal insulin

When switching from isophane insulin to analogue basal insulin, consider the following:

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

more insulin to cover blood glucose up to the evening meal.

High pre-lunch BGL

Case scenario

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

How would you control lunchtime hyperglycaemia?

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

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

Lunch bolus insulin

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

Morning basal insulin

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

Morning bolus insulin

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

Titrating insulin

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

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

As for basal insulins, the choice of bolus insulin is often guided by the injection device (Table 2). Alternatively, you may decide to stick to the same brand as the

Table 2. Bolus insulins

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

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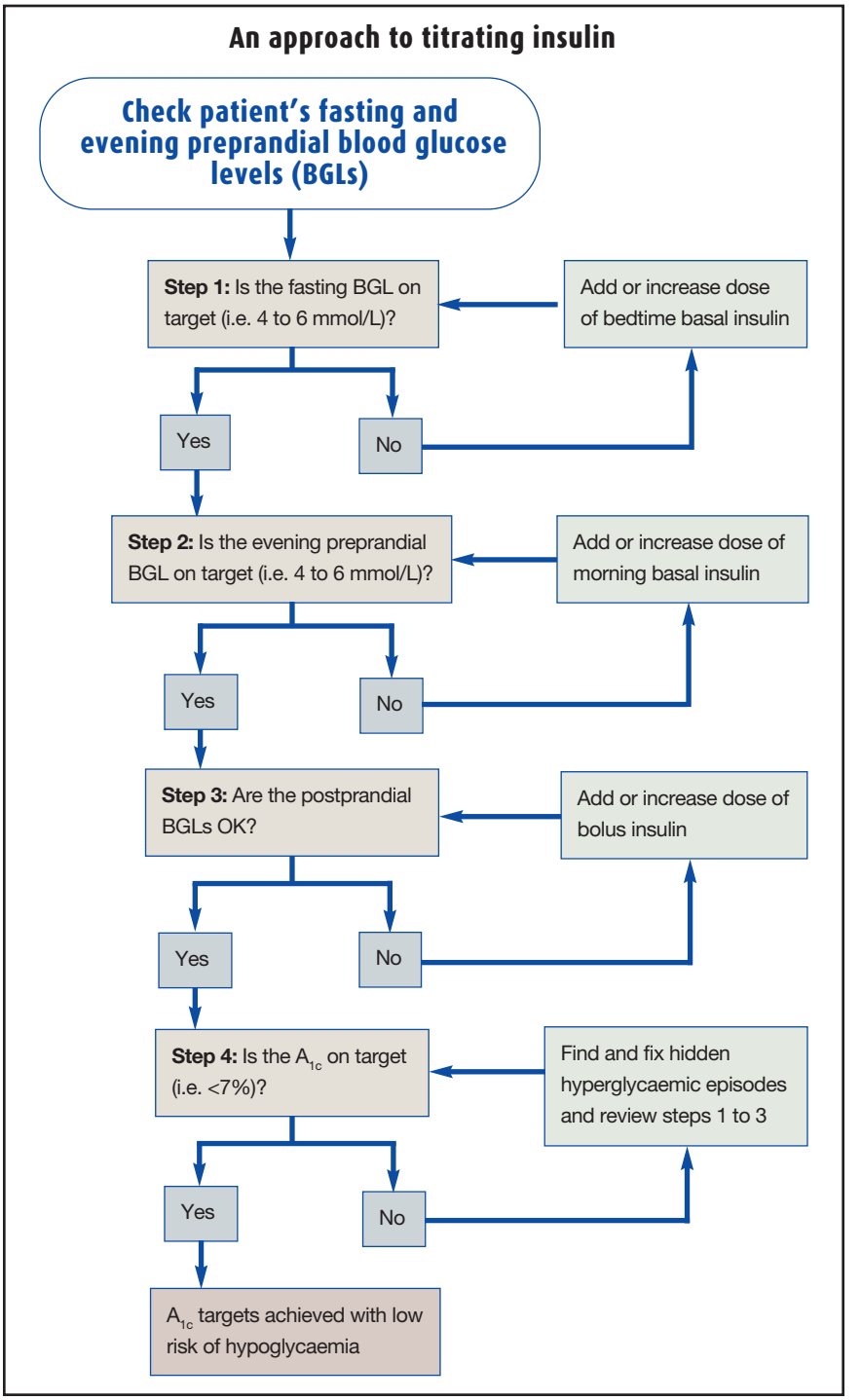
basal insulin. The safe and simple starting schedule is:

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

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

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

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



Conclusion

Most people with type 2 diabetes begin insulin therapy with one daily dose of basal insulin, usually at bedtime to control fasting BGL, and continue taking oral hypoglycaemic agents. As the diabetes progresses it is likely that evening hyperglycaemia will become a problem, necessitating the introduction of a morning dose of basal insulin. Bolus insulins may then be required to control any postprandial hyperglycaemic episodes.

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

The titration of insulin is summarised in the flowchart on page 51 and the box on this page. MT

Troubleshooting insulin problems: a summary

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

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

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