Achieving fasting and postprandial blood glucose control in type 2 diabetes

Until the availability of glycated haemoglobin, laboratory fasting plasma glucose was the measurement against which insulin doses were most commonly titrated. More recently, evidence has accumulated that self-monitored postprandial blood glucose may be at least as useful in adjusting treatment.

In 2005, the number of people in the UK known to have diabetes reached 2 million, an increase of 600 000 in 9 years, and a prevalence of over 3%. Of these, 85% have type 2 diabetes and, because of its insidious onset, there could be another million who have not yet been diagnosed (Diabetes UK, 2004, 2005). Several factors – an ageing population, rising obesity, sedentary lifestyles and high fat diets – explain this. Global prevalence of type 2 diabetes is predicted to increase to 366 million by 2030 (World Health Organization, 2005). Once described as 'late onset' diabetes, this condition is being increasingly diagnosed in younger adults, adolescents and children (American Diabetes Association, 2000).

Risk of complications

People with diabetes are at risk of small vessel (microvascular) and large vessel (macrovascular) complications that damage their physical health, worsen their quality of life and shorten their lives by up to 10 years. Rates of heart disease – the leading cause of diabetes-related death – are between 2 and 4 times higher in adults with diabetes than those without (Gerberding, 2005). Findings from two intervention trials published in the 1990s demonstrated clearly for the first time that blood glucose control (as evidenced by lowered glycated haemoglobin – HbA_{1c}) is central to preventing these complications. Compared with conventional therapy, intensive insulin therapy in the Diabetes Control and Complications Trial (DCCT) delayed the onset and slowed the progression of microvascular complications in patients with type 1 diabetes, with a suggestion of benefit on large vessel disease (The Diabetes Control and Complications (DCCT) Research Group, 1993). In the UK Prospective Diabetes Study (UKPDS), a more modest decrease in HbA_{1c} – from 7.9% to 7.0% – led to a 12% risk reduction in diabetes-related endpoints, mostly as a result of a 25% risk reduction in microvascular complications, and a 10% lower risk of diabetes-related death in patients with newly diagnosed type 2 diabetes (UK Prospective Diabetes Study (UKPDS) Group, 1998).

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In both trials, hypoglycaemia and weight gain were greater in the intensively treated group. The clinical evidence from these trials prompted the National Institute for Clinical Excellence (NICE) to recommend a target HbA_{1c} of between 6.5% and 7.5% for patients with type 2 diabetes and <7.5% for patients with type 1 diabetes (<6.5% for those at higher risk of complications) (NICE, 2002, 2004). These targets are difficult to achieve and maintain among patients with type 2 diabetes because of its progressive nature. This implies a need for constant monitoring and prompt intervention as control deteriorates, but doctors still behave as if the disease is static.

There is often, in practice, a significant delay before new or additional treatments are initiated in patients who are no longer achieving target HbA_{1c} on existing regimens. This is illustrated by a American study which showed the average patient accumulated several years of excess 'glycaemic burden' during their lifetime before control was achieved: nearly 5 years of an HbA_{1c} above 8.0% and 10 years above 7.0%. The mean number of months that elapsed at each stage before new or additional treatments were initiated ranged from 26.5 to 35.1. Extended periods of sub-optimal glycaemic control presumably put patients at increased risk of developing complications (Brown et al, 2004).

The importance of fasting and postprandial glucose control for overall HbA_{1c}

Early in the development of the disorder, release of insulin in response to food is blunted, leading to the development of postprandial hyperglycaemia (PPH) even if fasting blood glucose is well preserved; this is believed to further contribute to insulin resistance and a progressive drop in insulin production via 'glucose toxicity'.

Before the availability of HbA_{1c}, fasting plasma glucose (FPG) was routinely measured and used as a basis for titrating insulin, as in the original UKPDS protocol (Matthews et al, 2005) and it was assumed that FPG was the major determinant of HbA_{1c}, a view enshrined in an American Diabetes Association consensus statement (American Diabetes Association, 2001). However, in 1995 a study of 66 women with gestational diabetes challenged that view, showing that basing insulin dosage on postprandial blood glucose (PPBG) levels was superior.

The group that monitored PPBG had lower mean HbA_{1c} levels that measured blood glucose preprandially, accompanied by reduced neonatal hypoglycaemia and fewer deliveries by caesarean section among the infants (de Veciana et al, 1995). Since then, a debate has arisen as to whether FPG or PPBG is more important in determining HbA_{1c}. Some study results indicate that PPH contributes about 30–40% of the total daytime hyperglycaemia (Monnier et al, 2003). PPBG was found to be a better predictor of glycaemic control than FPG in patients with type 2 diabetes (Avignon et al, 1997; Caputo et al, 2001). The relationship between FPG, PPBG, HbA_{1c} and complications may be more complex than previously thought: data from several large epidemiological studies suggest correlations between PPH and cardiovascular complications including the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) which studied morbidity and mortality in more than 25 000 subjects (Davies and Chatterjee, 2004).

There is growing belief that PPH contributes an additional independent risk for development of heart disease. Several epidemiological studies conducted in the late 1990s have shown an association between PPH and cardiovascular disease and, more recently and tentatively, interventional studies suggest that treating PPH may reduce the development of atheroma (Ceriello, 2005). Monnier et al (2003) found postprandial glycaemic excursions in patients with well-controlled type 2 diabetes were a stronger predictor of cardiovascular disease than fasting hyperglycaemia (FH); however, FH plays a major role once HbA_{1c} rises above 8.4%. This suggests that control of PPH becomes more important as patients move closer to target HbA_{1c} levels. In contrast, as HbA_{1c} rises, FH becomes the major contributor to HbA_{1c} levels and the contribution of PPH reduces (*Figure 1*). This apparent shift in the contribution of FH and PPH to HbA_{1c} may account for the discrepancies in study findings (Monnier et al, 2003).

How to control the whole blood glucose profile

Whatever their relative contributions to HbA_{1c}, physicians agree that the best predictor of HbA_{1c} is mean blood glucose – affected by both fasting and postprandial levels – so achieving near-normal fasting and postprandial blood glucose levels is essential to overall glycaemic control (Parkin and Brooks, 2002).

For patients with type 2 diabetes, most oral hypoglycaemic agents will reduce postprandial glucose excursions but some are better than others; agents capable of stimulating a meal-related insulin release such as meglitinides and acarbose, which reduces carbohydrate absorption, are more helpful in reducing postprandial glucose fluctuations than long-acting sulphonylureas or metformin (Bell, 2001). The meglitinides (repaglinide and nateglinide) improve insulin secretion; they have a fast onset, short duration of action and a low risk of hypoglycaemia and weight gain but can only be used in patients with some remaining insulin secretion (Davies and Chatterjee, 2004; Kirby, 2005). As beta-cell function declines with progression of the disease, the replacement of missing secretion with exogenous insulin is required.

Insulin therapy aims to achieve near-normal glycaemic control without the unwanted side effects of weight gain and hypoglycaemia. Emulating normal physiology is thought to be the most promising route to this goal.

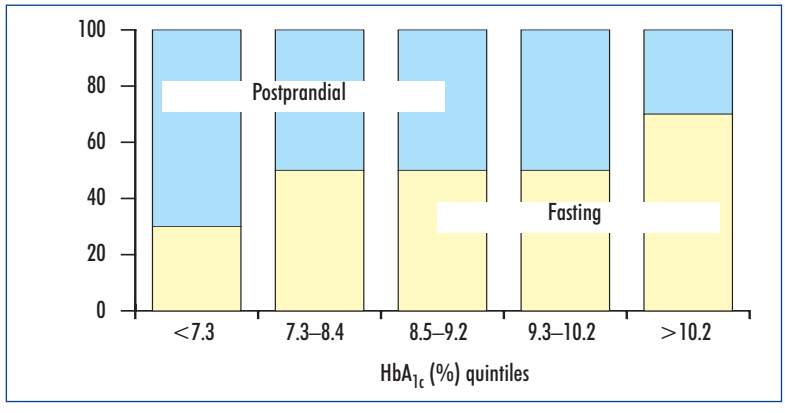
Optimal control in people with type 1 diabetes implies full insulin replacement with a 'basal-bolus' insulin regimen: a long-acting insulin to maintain fasting normoglycaemia plus pre-meal injections of shorter acting insulin to address postprandial spikes. However, the DCCT demonstrated the risks of over treatment (The DCCT Research Group, 1993).

How the new insulin analogues help

In 1996, the first of the rapid-acting insulin analogues, insulin lispro, was created by recombinant DNA technology, followed by insulin aspart. These are more rapidly absorbed and have a shorter duration of action than human soluble insulin, and are rapidly replacing it because of their greater ability to mimic an endogenous insulin prandial spike. When given immediately before a meal, they restrict postprandial glucose fluctuations more than soluble insulin administered 30 minutes before a meal; and because they are associated with a lower risk of nocturnal hypoglycaemia, there is no need for the bedtime snack often required after soluble insulin (Owens et al, 2001). The advantages of the rapid-acting analogues also include less weight gain and greater flexibility – rapid-acting analogues may be administered immediately before, or even after a meal, freeing patients from the inconvenience of predicting their mealtimes (Kunt, 2001; Owens et al, 2001). This flexibility enhances patients' quality of life, at home or in hospital, making insulin administration easier for patients with variable appetites and nurses awaiting the arrival of an unpredictable meal trolley.

A third rapid-acting insulin analogue, insulin glulisine, was launched in the UK in September 2005. In clinical trials, insulin glulisine demonstrated all the advantages of the other rapid-acting analogues – including equiva-

Figure 1. Relative contribution of fasting and postprandial glucose values to glycated haemoglobin (HbA_{1c}) in type 2 diabetes. From Monnier et al (2003).



lent postprandial glycaemic control in patients with type 1 and type 2 diabetes – and a similar safety profile (Garg et al, 2005). In one study, its effects occurred significantly earlier than insulin lispro in obese patients (with a body mass index (BMI) of >30 m/kg^2) (Heise et al, 2004), possibly of use in type 2 diabetes, where obese patients are more common.

Insulin glargine, the first basal insulin analogue, became available in the UK in 2002. Soluble at low pH, it forms microcrystalline aggregates subcutaneously at physiological pH, which slows its absorption. The result is a smoother profile with less of a pronounced peak. Its 24-hour metabolic effect more closely mimics the time profile of endogenous insulin secretion, unlike previous extended insulin preparations, the most commonly used of which was NPH (neutral protamine hagedorn) or isophane insulin, which shows a peak of activity after 4–6 hours followed by a steady decline (Heinemann et al, 2000; Lepore et al, 2000). Consequently, insulin glargine is associated with less nocturnal hypoglycaemia, less weight gain and greater flexibility in terms of injection timing than NPH, while providing equivalent control of HbA_{1c} (Yki-Järvinen et al, 2000; Rosenstock et al, 2001). Insulin glargine's time action profile means patients can choose at what time of day they can inject it (albeit at the same time each day) while NPH must be administered at night (or morning and night). Insulin glargine can be given either as part of a basal bolus regimen or in conjunction with oral hypoglycaemic agents, making it suitable for patients with type 1 and type 2 diabetes.

A second long-acting analogue, insulin detemir, was launched in 2004. Unlike glargine, its prolongation of action is provided by a 14-carbon chain covalently bound fatty acid moiety, which allows binding to serum albumin. Despite this, insulin detemir has similar properties to insulin glargine, possibly with a slightly shorter duration of action, but with less intra-individual variation. Clinical trials are currently being conducted on the use of detemir in type 2 diabetes. One recently published study supported detemir's ability to achieve blood glucose control targets with less hypoglycaemia at night and less weight gain than NPH insulin (Hermansen et al, 2006). Although not currently licensed for use in conjunction with oral agents, in practice it is used in much the same way as glargine.

Table 1. Correlation between glycated haemoglobin (HbA_{1c}) level and mean plasma glucose levels on multiple testing over 2–3 months

HbA_{1c}	Mean plasma glucose	
(%)	mg/dl	mmol/litre
6	135	7.5
7	170	9.5
8	205	11.5
9	240	13.5
10	275	15.5
11	310	17.5
12	345	19.5

Adapted from Rohlfing et al (2002)

It is necessary to target both fasting and postprandial blood glucose levels to achieve a glycaemic profile as close as possible to the profile of endogenous insulin. This is the rationale for basal bolus insulin therapy – a combination of short- or rapid-acting mealtime (bolus) insulin and intermediate- or long-acting basal insulin. It is, in effect, a full insulin-replacement regimen, and is used as such in type 1 diabetes, with at least four injections per day.

For people with type 2 diabetes, insulin therapy may be initiated more gradually as the disease progresses and glycaemic control deteriorates. As patients with type 2 diabetes often suffer from 'psychological insulin resistance' (Polonsky and Jackson, 2004) starting with one injection a day is more acceptable than multiple injections, so patients may be initiated onto a night-time injection of basal insulin in conjunction with oral agents. But as type 2 diabetes is a progressive disease, HbA_{1c} will gradually rise despite good FPG readings, as postprandial insulin secretion, even supported by oral agents, wanes over time. Indeed, some patients with long-standing type 2 diabetes may become very insulin deficient, resembling type 1 diabetes.

Twice daily pre-mixes – a ready mixed combination of a short-acting insulin and an intermediate-acting basal insulin – are an option for failing glycaemic control in patients with type 2 diabetes, or indeed in type 1. Injected before breakfast and before the evening meal, a typical premix would be made up of 30% short-acting and 70% intermediate-acting insulin. For example, for a premix given in the morning, the rapid-acting insulin provides a bolus for breakfast and the intermediate acting insulin peaks at midday and thus provides a degree of insulin supplementation for lunch. This regimen has neither the simplicity of a long-acting analogue or the flexibility of a basal bolus regimen. It is only suitable for those with relatively fixed habits, who must be taught to eat lunch whether or not they want to and that a night time snack is advisable to prevent nocturnal hypoglycaemia (Royal College of Nursing, 2004).

This lack of flexibility has led to basal bolus regimens being advocated in type 2 diabetes where basal insulin alone is not sufficient. In practice, these regimens are becoming increasingly commonplace as the condition becomes more widespread and physicians treat more aggressively in an effort to reduce complications and mortality and to meet clinical guidelines, although there are problems with older patients being moved to these complex regimens.

However, it may not be necessary to go directly from a single, basal insulin injection to four injections a day in a basal bolus regimen. In the AT.LANTUS (A Trial comparing Lantus Algorithms to achieve Normal blood glu-

cose Targets in patients with Uncontrolled blood Sugar) study, patients on glargine with one, two or three meal-time insulin injections showed similar improvement in control over basal alone, suggesting that it is not always necessary to supplement all the meals with insulin in all patients (Davies et al, 2005).

These data suggest that as oral agents and basal insulin gradually cease to maintain glycaemic control, oral agents can be replaced with a single pre-meal injection of rapid-acting insulin. The injection should be administered before the main meal of the day, i.e. the one producing the greatest postprandial excursion. If that is not sufficient to achieve control, a second meal can be supplemented, and so on. Using this stepwise approach, pre-meal bolus insulin may be given with two and then three meals a day as glycaemic control deteriorates. Although appealing as a strategy, and beginning to enter clinical practice in some centres under the name 'basal plus', this approach is only now being subject to formal testing in clinical trials, such as the OSIRIS (Opposing Step-by-Step Insulin Reinforcement to Intensified Strategy) study (http://clinicaltrials.gov/show/NCT00174642).

Case study

Mrs C, a 69-year-old widow, living alone, who has had diabetes for 15 years, had been on once-daily glargine for 2 years, titrated up against her fasting blood glucose. Despite good fasting records (5–6 mmol/litre), her HbA_{1c} had increased from 7.2% to 8.5% over 6 months, and when she was encouraged to test at other times, she was surprised to find her blood glucose in the high teens post-prandially and before bed. She switched to a twice-daily premixed 30/70 analogue insulin, but despite several visits to the diabetes specialist nurse, she found good blood glucose control elusive. Mrs C had night-time hypoglycaemic episodes at least once a week if she tried to reduce her bedtime glucose below 10 mmol/litre, and noticed weight gain for the first time in years. She was initially unwilling to move onto full basal-bolus therapy when this was offered as an alternative, because of the need for four injections per day. However, she did agree to revert to glargine, once daily in the evening with a rapid-acting analogue before her evening meal (6pm). Four months later, after titrating the dose of the meal-time rapid-acting insulin analogue she found she was regularly achieving a pre-bed glucose of 7 mmol/litre and a fasting blood glucose of 5–6 mmol/litre again without night time hypoglycaemia. Her HbA_{1c} had fallen to 7.6%, but she had mid-morning glucose readings of 8–10 mmol/litre. At the time of writing she had only just agreed to take a second meal-time bolus at breakfast time.

Conclusions

Evidence is emerging to show the different roles played by fasting and postprandial glucose levels and their contribution to the development of complications. As more people with diabetes live longer, it is vitally important to treat more patients ever more stringently to target HbA_{1c} to reduce the glycaemic burden of diabetes in order to prevent or delay the development of complications. The new rapid-acting insulin analogues, when given with long-acting basal insulin analogues, provide a form of insulin supplementation that more closely mimics an endogenous insulin profile, and consequently are effective at controlling the blood glucose profile ever more tightly in either type of diabetes. Basal insulin supplemented in a step-wise fashion with a rapid-acting analogue may provide an acceptable framework to intensify glucose control over time to cope with the progression of type 2 diabetes. *Figure 2* outlines important considerations when caring for patients with diabetes as inpatients. BJHM

Figure 2. Taking care of inpatients with diabetes.

The rising prevalence of diabetes and use of insulin in type 2 diabetes means more routine admissions will be insulin treated and will often be cared for by hospital staff who do not have diabetes specialist experience. Considering the points below may help prevent erratic blood glucose control under those circumstances.

- To ensure that adjustments to insulin therapy are most likely to produce good overall control, decisions should be based on a recent glycated haemoglobin (HbA_{1c}) and examination of the whole glucose profile (usually from the routine ward glucose monitoring), ideally over several days, and not on single, random blood glucose measurements. If HbA_{1c} is not available, it is reasonable to obtain one.
- Both post-prandial and fasting hyperglycaemia contribute to elevated HbA_{1c}. Look for evidence of both during a hospital stay: was a raised glucose likely to have been pre- or postprandial? This may guide your treatment decisions during the stay and the outpatient diabetes management after discharge.
- Respond to abnormal blood glucose results by increasing the insulin dose likely to control that value on the following day. This is easier on a basal bolus regimen than with premixed insulin. In type 2 diabetes, controlled by insulin and tablets, an increase or decrease of 20% in each insulin dose is often a good balance between caution and effectiveness. If the patient is on insulin alone, the dose changes are probably better to be around 10%.
- Optimal control implies fasting blood glucose below 6 mmol/litre and 2-hour postprandial glucose below 9 mmol/litre, but no readings under 4 mmol/litre or symptomatic hypoglycaemia. Poor control is represented by blood glucose measurements in double figures or an HbA_{1c} of more than 7.5%.
- Admissions to other specialties with poorly controlled diabetes should be referred to the diabetes team for a treatment review post discharge if that is feasible.
- Treatment with steroids can exaggerate postprandial blood glucose measurements, raising them out of all proportion to fasting plasma glucose. There may be a lag of a day or two when steroids are introduced or withdrawn before these effects are seen.
- It is especially important to stabilize blood glucose levels around surgery to improve outcomes. However, the withholding of food, anaesthesia and surgery itself can combine to upset glycaemic control.
- Your hospital will have a variable intravenous insulin and dextrose infusion protocol to cover starvation for surgery. Use it unless the procedure is trivial with minimal fasting.
- A peer-reviewed checklist of pre- and postoperative care for patients with diabetes can be found at http://www.patient.co.uk/showdoc/40024475/ . This is a general checklist and intended as a guide only.
- In general, the use of single fixed dose boluses of subcutaneous insulin, e.g. 6 units of Actrapid, to respond to high blood glucose measurements is to be avoided. Likewise subcutaneous 'sliding scales' do not allow good glucose control. These tend to cause episodes of hypoglycaemia and subsequent raised blood glucose measurements.
- If the patient has poor control, and you want to improve it rapidly, use an intravenous insulin and dextrose infusion overnight to achieve good fasting blood glucose, then start or restart a subcutaneous insulin regimen. Returning the patient to subcutaneous insulin is easier on a basal bolus regimen.

Conflict of interest: As a research fellow, Dr Robertson was supported by Novonordisk in carrying out phase 1 (preclinical) trials of several rapid acting insulin analogues. Dr Robertson is UK Chief Investigator for the OSIRIS study, and was a participating investigator in the AT.Lantus study. He has accepted honoraria and travel bursaries for speaking at academic meetings from sanofi-aventis, Eli Lilly and Novonordisk, and has consulted for Novonordisk, Eli Lilly and sanofi-aventis on insulin products within the last 5 years. Dr Robertson has been given secretarial support from sanofi-aventis to write this article, but the company had no editorial input.

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KEY POINTS

- A global epidemic of diabetes is underway affecting more than two million people in the UK; the vast majority of these have type 2 diabetes, a progressive condition in which glycaemic control deteriorates over time.
- If patients are to avoid developing the micro- and macrovascular complications associated with diabetes, treatment regimens must be regularly reviewed and adjusted to compensate for deteriorating control.
- Insulin was traditionally titrated against fasting plasma glucose but recent research shows postprandial blood glucose may be more important in determining glycated haemoglobin levels and may even be an independent risk factor for atheroma.
- Modern insulin analogues are more effective at controlling postprandial blood fluctuations than traditional insulin preparations.
- Adjustments to insulin should be based on regular monitoring of regular monitoring of pre- and postprandial capillary blood glucose over several days and not on single, random measurements.