



2: Recent advances in therapy of diabetes

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More individualised and physiological therapy is now possible

THE DISCOVERY OF INSULIN and its introduction as therapy for type 1 diabetes in the early 1920s was understandably thought to have resolved the management of this fatal disease. However, within a few decades the spectre of diabetes complications arose, and it became apparent that more sophisticated therapy was needed. Since then, a wide range of insulin preparations and therapeutic strategies have been developed in attempts to mimic natural insulin profiles, while bovine and porcine insulins have been largely replaced by recombinant human insulin. Most recently, recombinant DNA technology has allowed the insulin molecule itself to be modified to create insulins with vastly altered pharmacokinetic characteristics (the insulin analogues). These, along with new modes of delivery and monitoring, now hold promise of even more individualised and physiological treatment.

In the second half of the 20th century, type 2 diabetes was recognised as a disease, along with its related disorders, including the metabolic syndrome. Type 2 diabetes is now increasing rapidly in prevalence and also requires new therapeutic strategies.

Type 1 diabetes

In the past decade, two major advances have improved the care of patients with type 1 diabetes. First, we understand the unequivocal relationship between metabolic control and vascular complications;¹⁻⁴ suboptimal blood glucose control has a lasting harmful effect even if control improves later. Second, the development of new forms of insulin with more rapid onset or longer duration of action (insulin analogues) and new forms of delivery (eg, continuous pumps and aerosol sprays), as well as advances in glucose monitoring, provide more options for those affected.

Intensive diabetes management

Because of the relationship between suboptimal glycaemic control and vascular complications, intensive management

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ABSTRACT

- As suboptimal blood glucose control has a lasting harmful effect even if control improves later, intensive insulin therapy to minimise hyperglycaemia is now recommended for all patients with type 1 diabetes.
- The new rapid- and long-acting insulin analogues offer more physiological insulin profiles than traditional insulin preparations.
- Continuous insulin infusion ("pump therapy") may provide a solution for some patients with frequent hypoglycaemia or hypoglycaemic unawareness.
- Continuous blood glucose monitoring reveals postprandial hyperglycaemia and asymptomatic nocturnal hypoglycaemia and may be especially useful for programming overnight basal insulin rates for pump therapy.
- In type 2 diabetes, management should change with disease progression; introduction of insulin should not be delayed if metabolic control becomes suboptimal.

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to minimise hyperglycaemia is now recommended for all patients. This may include more frequent administration of insulin (up to four times daily) or use of different insulin types (eg, rapid- and long-acting insulin analogues), as well as more frequent blood glucose measurements and changes to insulin dose than in conventional therapy.

Intensive schedules need to be individualised to suit patient age and lifestyle. For example, adults and adolescents generally need intermediate-acting insulin before bed for night-time control. Some school-aged children need short-acting insulin at afternoon tea rather than lunch-time to prevent late-afternoon hyperglycaemia, while many pre-school-aged children can be managed with one dose of intermediate-acting insulin in the morning and small doses of rapid-acting insulin analogues (see below) to prevent hyperglycaemia later in the day. The imminent availability of long-acting insulin analogues will change these schedules considerably. Insulin pumps may be useful for some patients with frequent hypoglycaemia or hypoglycaemic unawareness.

Intensive therapy is more demanding for patients and their families, and adherence is obviously critical to its success. Patient views are therefore central to management decisions. For example, an adolescent who struggles to

1: Case report — an adolescent with type 1 diabetes

Presentation: A 13-year-old high school student with a 5-year history of type 1 diabetes presented for follow-up at a diabetes clinic. She had been treated since diagnosis with twice-daily injections of short-acting plus intermediate-acting human insulin (1.3 U/kg per day, Protaphane/Actrapid or Humulin NPH/Humulin R). She monitored her blood glucose level approximately once daily and reported minimal symptomatic hypoglycaemia. She played badminton on most evenings.

Investigations: Her HbA_{1c} level was 9.7%, indicating poor glycaemic control. Body mass index (BMI) was 19 kg/m² (RR, 20–25 kg/m²).

Management: After discussion with the endocrinologist and diabetes educator, the girl agreed to try a more intensive basal-bolus regimen injected with a pen delivery device to improve her glycaemic control. This regimen comprised:

- an intermediate-acting human insulin before bed (Protaphane or Humulin NPH); and
- a rapid-acting insulin analogue three times daily before meals (NovoRapid or Humalog).

She was asked to increase blood glucose monitoring to at least three to four times daily (before and after eating), and was scheduled for follow-up after 3 months.

3-month follow-up: Her HbA_{1c} level had risen to 10.8%, and BMI had fallen to 17 kg/m². Menstrual cycles remained regular. She found it difficult to adhere to the insulin schedule and rarely took lunchtime insulin at school.

Further management: Her insulin schedule was changed to three times daily, comprising:

- a mixture of short- and intermediate-acting human insulin in the morning (Protaphane/Actrapid or Humulin NPH/Humulin R);
- a rapid-acting insulin analogue before the evening meal (NovoRapid or Humalog); and
- an intermediate-acting human insulin before bed (Protaphane or Humulin NPH).



- Doses were to be adjusted frequently depending on blood glucose profile, expected food intake and activity. The importance of monitoring blood glucose frequently was repeated. She also saw a diabetes educator and a dietitian at this visit to assess her current diet and to help individualise the regimen accordingly. Her family was to have weekly telephone contact from the diabetes educator for support in insulin adjustment, and she was to have follow-up clinic review in 6 weeks.

■ *Blood glucose control may deteriorate during adolescence because of physiological changes associated with puberty and difficulties with adherence.*

■ *Because of the relationship between poor glycaemic control and vascular complications, intensive management should be offered to all people with type 1 diabetes.*

■ *As an intensive schedule is often difficult to introduce in adolescence, most units caring for this*

age group begin this schedule from diagnosis. When introducing an intensive schedule, a diabetes educator and dietitian experienced with adolescents should be involved, with frequent contact to help adherence; in this case, 3-monthly review was inadequate.

■ *Deteriorating glycaemic control, indicated by a rising HbA_{1c} level with the initiation of intensive diabetes management, suggests poor adherence.*

■ *A three-times-daily insulin schedule avoids a lunch-time insulin dose at school and, as adherence was already a problem for this patient, might be the best compromise at this stage.*

■ *While the girl's weight loss may have been related to the deterioration in metabolic control, the possibility of an eating disorder should be considered. If weight loss continued, referral to a psychologist or psychiatrist might be advisable.*

comply with two injections a day is unlikely to manage four injections (see case report, Box 1). However, for most patients, the demands of achieving good control are less than the consequences of poor control.⁵ In adolescents, good control improves quality of life and reduces the burden perceived by their parents.⁵

The limiting factor preventing ideal glycaemic control remains hypoglycaemia. Glucagon secretion is blunted early in the course of type 1 diabetes, increasing the patient's vulnerability to hypoglycaemia. Furthermore, the blood glucose threshold for release of catecholamines, which both stimulate glucose production and produce warning symptoms such as sweating and trembling in response to hypoglycaemia, is lowered in patients with better glycaemic control, even more so during sleep.⁶ Continuous glucose monitoring devices reveal the frequency of nocturnal hypoglycaemia and the limitations of conventional blood glucose monitoring. Both the new insulin analogues and continuous subcutaneous insulin therapy hold promise of improving control without the attendant risk of hypoglycaemia.

Insulin analogues

In the past, the pharmacokinetic characteristics of insulin preparations have been modified by mixing with substances that delay absorption (eg, protamine and zinc) and by varying crystal size. Recombinant DNA technology has now made possible the creation of analogues of human insulin with altered pharmacokinetic characteristics (Box 2).

Rapid-acting analogues: These are also known as rapid-onset and ultra-short-acting insulins and include insulin aspart and insulin lispro. They were created by modifying the amino acid sequence of the insulin B chain (substituting aspartic acid for proline at position 28 [aspart] and reversing proline and lysine at positions 28 and 29 [lispro]).

These analogues have the advantages that:

- they follow better the rise in blood glucose level after eating than conventional short-acting insulins, thereby reducing postprandial hyperglycaemia and between-meals hypoglycaemia;
- their very rapid onset of action allows them to be injected immediately before meals or even after eating,

which is especially useful in young children with erratic eating patterns.

Their disadvantages are:

- shorter duration of action than traditional short-acting human insulins, which could cause preprandial hyperglycaemia.

The short-acting analogues are available on the Pharmaceutical Benefits Scheme.

Long-acting analogues: These were created by substituting and adding amino acids to the insulin molecule (glargine) and by adding a fatty acid chain, which enhances binding to albumin (detemir).

The long-acting analogues have the advantages of:

- more reproducible absorption than conventional long-acting insulins;
- a flat dose profile with a low peak of action, which provides more predictable background control than the intermediate-acting insulins, without the unwanted peaks of action around lunchtime and during the night.

Initial studies indicate that the long-acting analogues reduce the risk of nocturnal hypoglycaemia and produce a modest reduction in fasting blood glucose levels compared with intermediate-acting preparations.⁷ Neither is as yet available on the Pharmaceutical Benefits Scheme (PBS). There are few data on the relative benefits of administration by pump versus multiple daily injections for glargine or detemir as the basal insulin, but better night-time blood glucose control with pump therapy has recently been described.⁸

New delivery systems

Pump therapy: The effectiveness of continuous subcutaneous insulin infusion (pump therapy) has been rediscovered (Box 3). First used in the 1970s and 1980s, pump therapy has been reintroduced with improved technology. Small amounts of a rapid-acting insulin analogue are infused, usually into the abdomen or buttocks, at a basal rate, which can be varied, with extra boluses calculated for each meal and snack. The major advantages are less variable absorption and improved insulin pharmacokinetics. Varying the basal rate can help regulate overnight blood glucose levels. Pump therapy is suitable for motivated patients, particularly those with frequent hypoglycaemic episodes or hypoglycaemic unawareness, as most studies show reduced hypoglycaemia.^{9,10} Because the infused insulin is rapid-acting, mechanical interruption of the pump can rapidly lead to ketosis, which is of particular concern in pregnancy. Pump therapy must therefore be accompanied by frequent blood glucose monitoring. Private health insurance companies now subsidise the cost of the pump and some consumables, but there is no government funding. As for all therapies, it is essential that the patient is central to the choice of pump therapy. This is also important when the patient is a child or adolescent, whose views may differ from those of their parents.

Aerosols: Aerosolised insulins for delivery by inhalation are under active investigation, with Phase III studies completed. These insulins provide effective cover for meals in combina-

2: New and commonly used insulin preparations in Australia*

Preparation	Insulin type	Onset of action	Maximum effect (h)	Duration of action (h)
<i>New insulin analogues[†]</i>				
Rapid-acting analogues				
Humalog	Lispro	15 min	1–2	3.5–4.5
NovoRapid	Aspart	10–20 min	1–3	3–5
Biphasic analogue mixtures				
Humalog Mix25	Lispro + lispro protamine suspension	15 min	2	24
NovoMix 30	Aspart + aspart protamine crystallised	10–20 min	1–4	24
Long-acting analogues [‡]				
Lantus	Glargine	1–2 h	6 + [§]	24 +
Not yet named	Detemir	1–2 h	6–8	20
<i>Conventional human insulins</i>				
Short-acting insulins				
Actrapid	Neutral	30 min	2.5–5	8
Humulin R		30 min	2–4	6–8
Intermediate-acting insulins				
Humulin NPH	Protamine suspension	1 h	4–10	16–18
Protaphane		1.5 h	4–12	24
Humulin L	Zinc suspension	2 h	6–12	24
Monotard	(lente)	2.5 h	7–15	22
Long-acting insulins				
Humulin UL	Microcrystalline zinc suspension (ultralente)	2 h	6–20	24 +
Ultratard		4 h	8–24	28
Biphasic mixtures				
Humulin 30/70	Mixture of a neutral insulin	30 min	2–12	16–18
Mixtard 30/70	and a protamine suspension	30 min	2–12	24
Humulin 20/80		30 min	1–9.5	17–19
Mixtard 20/80		30 min	2–8	24
Humulin 50/50		30 min	2–12	16–18
Mixtard 50/50		30 min	4–8	24

* Most preparations are available in a variety of presentations, including vials, cartridges for insulin pens, and pre-filled pens or devices. Humalog and Humulin preparations are manufactured by Eli Lilly, Lantus by Aventis, and all other listed preparations, including detemir, by Novo Nordisk.

[†] None of the insulin analogues are registered for use in pregnancy.

[‡] The long-acting analogues are not currently registered in Australia.

[§] No defined peak of action.

tion with once-daily, long-acting, subcutaneous insulin. However, aerosol delivery requires six times as much insulin for the same effective dose as subcutaneous injection, which may create a cost barrier to widespread use. Also, the long-term safety of delivering large amounts of insulin to the alveolae is not known.

At present, all systems deliver insulin to the systemic circulation rather than the enteroportal circulation. Sys-

3: "Pump therapy" (continuous subcutaneous insulin infusion)



Insulin is infused into the abdomen or buttocks by a programmable pump which can be worn on the belt similarly to a pager.

temic delivery contributes to the insulin resistance associated with obesity and adolescence and is a major barrier to physiological insulin replacement. However, a method of accessing the enteroportal circulation is not currently in sight.

New monitoring systems

Continuous blood glucose monitoring: Intermittent measurements of capillary blood glucose give a limited glimpse of blood glucose levels, which may fluctuate widely over 24 hours. The recent introduction of systems for continuous blood glucose monitoring is an exciting advance^{11,12} (Box 4). Continuous monitoring reveals post-prandial fluctuations in glucose level and asymptomatic nocturnal hypoglycaemia, and is likely to be especially useful in programming overnight basal insulin rates for pump therapy. Continuous monitoring systems available in Australia measure interstitial blood glucose via an indwelling cannula in the abdomen or buttocks. However, they are expensive (\$5000 or more) and, at present, are most applicable for use by diabetes centres which lend devices to patients for restabilisation. Devices under investigation have alarms to alert patients to glucose levels outside a target range and provide immediate read-outs.

Non-invasive blood glucose monitoring: Frequent automatic glucose readings can be obtained non-invasively through the process of reverse iontophoresis, in which a low electric current pulls glucose molecules through the skin for collection in a gel disc. A device that is worn like a wristwatch is approved for patients aged over 7 years in the United States, but its cost (about US\$1000 for the device and more than US\$100 per disposable 12-hour sensor) limits more widespread use. It is not yet available in routine practice in Australia.

HbA_{1c} measurement: Measurement of glycosylated haemoglobin (HbA_{1c}) remains the criterion standard to judge the outcome of diabetes management. Rapid measurement with a desktop device expedites assessment and education. Results of longitudinal studies now allow accurate prediction of the risk of vascular complications for a given HbA_{1c} level^{3,4} (Box 5). This can be very useful when counselling patients. For example, a teenager can be advised that large trials show that reducing the HbA_{1c} level from 9% to 8% and maintaining the reduction during adolescence reduces the risk of proliferative and severe non-proliferative retinopathy in young adulthood by 70%–80%.³

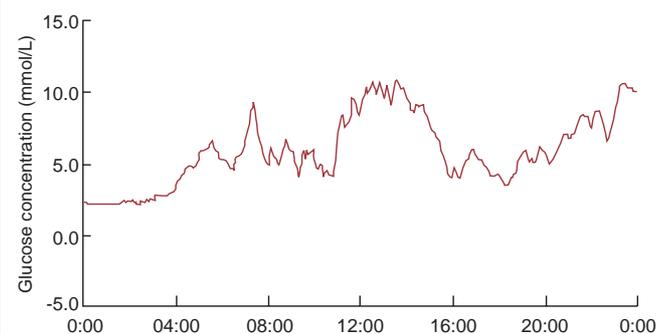
Other advances

Education and psychological support: With the advent of intensive therapy and its greater demands on patients and their families, counselling and education are becoming even more important in achieving compliance, particularly in adolescents. However, as long-term risk of vascular complications can be predicted more accurately from HbA_{1c} level, it is easier for doctors to counsel and encourage intensive management.¹⁻⁴ Furthermore, as doctors have become more certain about the need for intensive management, it is our impression that patients and their families have accepted and coped better with it. Indeed, mean HbA_{1c} levels in Australian children have improved from 10% in the 1980s to around 8% in 2003.¹⁴

Coping-skills training has been shown to improve metabolic control and quality of life in adolescents.¹⁵ This intervention, like all successful interventions in type 1 diabetes, needs to be intensive, and support must be sustained.

The indispensable role of the diabetes educator and dietitian in the multidisciplinary team has long been recognised. Dietary management and education is now more comprehensive and includes the concept of the glycaemic indices of food.¹⁶ Educators' roles are becoming more specialised, both for different age groups and, as technology progresses, for different monitoring and delivery systems.

4: Continuous blood glucose monitoring



Blood glucose profile obtained by continuous subcutaneous monitoring in an adolescent with type 1 diabetes, showing night-time hypoglycaemia (blood glucose level <3.0 mmol/L) which was asymptomatic.

5: Glycosylated haemoglobin (HbA_{1c}) levels and diabetes complications

- In normal glucose tolerance, HbA_{1c} level is usually < 5%.
- In diabetes, an HbA_{1c} level > 8% indicates poor glycaemic control and a need to assess therapy and adherence.
- A decrease in HbA_{1c} level of 1 percentage point has been shown to lead to:
 - a 10% reduction in microvascular complications in type 2 diabetes (UKPDS trial¹³) and
 - a 20%–30% reduction in microvascular complications in type 1 diabetes (DCCT trial³), with associated less significant reductions in macrovascular complications.
- In treating diabetes, the benefits of decreasing HbA_{1c} level must be weighed against the risk of side effects and the ability of the patient to comply; thus, the “target” HbA_{1c} level must be individualised.
- HbA_{1c} levels < 6% are very difficult to achieve in diabetes without serious side effects, such as life-threatening hypoglycaemia.

New use of old drugs: Adding metformin to the treatment regimen for type 1 diabetes can improve metabolic control by reducing insulin resistance, a problem in both obese patients and adolescents with diabetes, in whom the physiological insulin resistance of puberty is exaggerated, necessitating high insulin doses.¹⁷ However, metformin is suitable only for patients with low alcohol intake and normal renal and hepatic function who remain compliant with insulin therapy.

Glucagon in small frequent doses (<0.15 mg up to 6-hourly) can prevent hypoglycaemia (and resulting hospital admissions) in patients with reduced oral intake, including children with viral gut infections.¹⁸

Type 2 diabetes

Type 2 diabetes mellitus generally forms part of the “metabolic syndrome”, which is characterised by insulin resistance, obesity and a range of cardiovascular risk factors, as discussed previously in this series.¹⁹ Advances in management of type 2 diabetes include recognition of the need for early and aggressive management of insulin resistance and associated abnormalities, such as dyslipidaemia, hypertension and albuminuria.

Therapy for type 2 diabetes

Therapy for type 2 diabetes should be tailored to the pathological process that is most prominent at different stages of the disease (see case report, Box 6).

Increase insulin sensitivity: Early in the disease process, the aim should be to target insulin resistance with diet and exercise plus metformin therapy. A weight loss of 5 kg leads to a 25%–50% reduction in insulin resistance (J Prins, unpublished data). Metformin is tolerated by most patients if started at a low dose (eg, 250–500 mg/day), which is slowly increased depending on blood sugar response and tolerance.

The thiazolidinediones (rosiglitazone and pioglitazone) are newer insulin-sensitising agents which are effective, but

have the disadvantage of causing some weight gain and fluid retention. However, unlike metformin, they are safe in patients with renal impairment. They are widely used overseas but are not currently available on the PBS.²⁰

Increase circulating insulin: If strategies to increase insulin sensitivity are ineffective, the next step is to increase circulating insulin level. Oral agents currently available in Australia for this purpose are the sulfonylureas and the newer glitinides. Metformin should be continued if the patient is obese.

As sulfonylureas are potent and long-acting, hypoglycaemia is a significant clinical problem, but can be avoided with careful dose titration. Sulfonylureas cause weight gain of a few kilograms in most patients and lose efficacy with time, either because of increasing insulin resistance (usually due to the weight gain) or “secondary” pancreatic β -cell failure. Other than half-life differences, there is little to distinguish later-generation sulfonylureas.

Glitinides (eg, repaglinide) are short-acting drugs that increase insulin secretion. They are well tolerated but less potent in clinical practice than the sulfonylureas. Their advantage lies in their short half-life, making hypoglycaemia less common, but pre-meal dosing is a disadvantage for many patients. Glitinides are not currently available on the PBS.

Exogenous insulin: If diabetic control remains, or becomes, suboptimal when taking oral combination therapy with metformin and a sulfonylurea, then insulin is indicated.^{21,22} As evidence supporting the benefits of good diabetic control is now overwhelming,¹³ any delay in introducing insulin in these patients is now considered unacceptable. It is important to educate patients that insulin is usually necessary because of natural progression of the disease and not necessarily because of any “failure” on their part. It is therefore advisable to introduce the concept well before necessary. A good “selling point” is that insulin often substantially improves how patients feel.

With currently available insulin preparations and administration devices, it is straightforward to develop an acceptable “physiological” insulin-replacement regimen for almost all patients.^{21,22} Newer analogue insulins (including mixtures) have a definite place in the management of type 2 diabetes and contribute to the excellent choices available.

There is little point in continuing sulfonylurea or glitinide therapy after introducing insulin. Advantages of ceasing oral agents are simplification of therapy, less chance of drug interaction, reduced costs and improved compliance. However, metformin should be continued in obese patients, as it helps maintain weight and allows lower insulin doses to be used. Pioglitazone is the only insulin-sensitiser available for combination with insulin in Australia for patients with renal impairment.

Monitoring of type 2 diabetes

With recognition of the importance of blood sugar control in type 2 diabetes, aggressive monitoring is now essential. Monitoring of HbA_{1c} level is central to management of type 2 diabetes and may be simplified by the new desktop

6: Case report — management as type 2 diabetes progresses

Presentation: A 51-year-old man with a 6-year history of type 2 diabetes presented to his general practitioner. He was an ex-smoker, with moderate alcohol consumption. He was taking metformin (500 mg twice daily) and was not prepared to consider changes in diet or exercise, despite considerable effort from the GP and a dietitian.

Examination and investigations: He weighed 102 kg, with body mass index 32 kg/m² (reference range [RR], 20–25 kg/m²), and waist circumference, 110 cm (RR, < 94.0 cm). His glycosylated haemoglobin (HbA_{1c}) level was 7.5%, reflecting good glycaemic control.

Management: The metformin dose was increased to 1 g twice daily. He again declined to modify diet or exercise. He was instructed to measure his fasting blood glucose level at least twice daily and to return for early review if readings were regularly over 8 mmol/L.

2-year review: He remained compliant with metformin therapy, but his HbA_{1c} level had risen to 10%, and his blood pressure was 160/100 mmHg. Lipid levels were within the reference ranges. He still refused to modify diet or exercise. He had not been measuring blood glucose levels.

Management: The GP reiterated the importance of monitoring fasting blood glucose levels at home. A sulfonylurea and an angiotensin-converting enzyme (ACE) inhibitor were added to the regimen; metformin was continued.

3-year review: The HbA_{1c} level had decreased to 7.8%, and blood pressure to 130/80 mmHg, but the patient had gained weight (110 kg). He was taking the maximum tolerated dose of metformin (1 g twice daily) and the maximum dose of the sulfonylurea.

Management: Diet and exercise changes were again suggested, with no success.

4-year review: The HbA_{1c} level had risen to 8.9%.

Management: Insulin was judged to be necessary. Treatment choices were to:

- Add intermediate-acting insulin at night (eg, Humulin NPH or Protaphane) at an initial dose of 10–20 U, to be titrated up based on early-morning blood glucose level, with continuation of sulfonylurea and metformin; or
 - Cease sulfonylurea, continue metformin and introduce insulin either twice daily (possibly using premixed insulin, including analogue mixtures) or four times daily (with regimens similar to those for type 1 diabetes); total daily insulin dose is often around 1 U/kg.
- *This patient demonstrates the need to change management as disease progresses.*
- *Metformin was the initial drug of choice, as the major abnormality at that time was insulin resistance.*
- *An alternative second-line therapy to a sulfonylurea would be a thiazolidinedione, which would have the advantage of further targeting the insulin resistance, but, currently in Australia, the choice is limited by prescribing restrictions and cost.*
- *If metabolic control is suboptimal, introduction of insulin should not be delayed.*



measuring device. It is noteworthy that 1–2 days of hyperglycaemia (eg, during an infection) will increase HbA_{1c} level for some weeks. HbA_{1c} level is falsely low in some haemoglobinopathies and in states of increased red cell turnover, such as haemolysis. In these cases, the level of fructosamine (glycosylated albumin) can be measured. This reflects glycaemic control over weeks, rather than the 2–3 months reflected by HbA_{1c} level. Its assay is less reliable, and it is not indicated routinely.

Home blood glucose monitoring is crucial for diabetic control. In type 2 diabetes, insulin resistance makes good control of postprandial blood sugar very difficult. We therefore recommend that fasting blood glucose level be recorded at least twice daily at different times (before meals and before bed) during the week so that patterns of glucose control can be identified.

Drugs on the horizon

Insulin analogues: Many of the new insulin analogues will have a place in management of type 2 as well as type 1 diabetes.

Dual PPAR γ / α agonists: The nuclear hormone receptor PPAR γ (peroxisome proliferators-activated receptor) is involved in glucose and, to a lesser extent, lipid metabolism and is a target of the thiazolidinediones (glitazones). Drugs

are currently under trial which act both on this receptor and a related receptor involved in lipid metabolism, which is targeted by the fibrates. These dual PPAR γ / α agonists will probably have an important role in managing type 2 diabetes and the metabolic syndrome within a few years.

Orlistat: This lipase inhibitor is currently indicated for use in obesity. Clinical trials have demonstrated its usefulness as an insulin-sensitising agent, with the added benefit of weight management.²³ Overall efficacy appears similar to that of metformin or sulfonylurea.

Insulin secretagogues: These include the gut-derived hormones (incretins), such as glucagon-like peptide-1 (GLP1) and gastric inhibitory peptide. GLP-1 analogues and receptor agonists are currently under clinical trial and show definite promise for patients with type 2 diabetes. Administration is parenteral, but initial trial results demonstrate efficacy in blood sugar control, minimal risk of hypoglycaemia, and the associated benefit of weight loss. A related approach is oral administration of dipeptidase IV inhibitors, which effectively increase GLP-1 levels.²⁴

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