CPD Module 3

Insulin therapy in type 2 diabetes

Jill Hill

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Insulin therapy is ultimately required by many people with type 2 diabetes. Unlike in type 1 diabetes, the aim of insulin therapy in people with type 2 diabetes is initially to supplement the endogenous insulin produced by pancreatic beta-cells against a background of insulin resistance. Over time, the progressive nature of type 2 diabetes necessitates the intensification of the insulin regimen. This article focuses on the different types of insulin and insulin regimen currently in use in the UK for people with type 2 diabetes, and summarises the current related clinical guidance and evidence.

Learning objectives

After reading this article, the participant should be able to:

1. Explain why insulin requirements differ in type 1 and type 2 diabetes.
2. Outline the different types of insulins and explain why they are used in different ways.
3. Describe the various insulin regimens used by people with type 2 diabetes, with an appreciation of the pros and cons of each.

Key words

- Insulin
- Insulin regimens
- Hypoglycaemia
- Weight gain

Type 2 diabetes is a progressive condition characterised by initial insulin resistance followed by gradual loss of beta-cell insulin secretory ability. The UKPDS (UK Prospective Diabetes Study) demonstrated that no matter how type 2 diabetes is treated, there is a progressive increase in HbA_{1c} (UKPDS Group, 1995). This means that oral antidiabetes drugs (OADs) become less effective over time, and eventually most people with type 2 diabetes need insulin to achieve or maintain their ideal HbA_{1c} level (Turner et al, 1999; Nathan et al, 2006). The UKPDS confirmed that glycaemic control of a level nearing that of people without diabetes reduces the risk of microvascular and macrovascular complications and mortality (UKPDS Group, 1998; Holman et al, 2008), and insulin therapy will therefore be necessary to achieve this in many cases. *Box 1* provides some key facts and practical considerations relevant to insulin therapy in type 2 diabetes.

As insulin therapy is likely to be ultimately required in people with type 2 diabetes, it should be discussed early after diagnosis so that, when it is needed, it is not seen as failure of self-management or a punishment for non-adherence. In the author's experience, people may be fearful of starting insulin as a result of previous experiences of older members of the family (for example, a grandmother using glass syringes with large needles, who started insulin after amputation), a fear of needles, concern about possible hypoglycaemia and weight gain, or the perception that they now have "serious diabetes" (in contrast to "mild diabetes" controlled by diet and tablets). These concerns need to be addressed early to avoid delay in starting insulin therapy when it is needed.

Unlike in type 1 diabetes, which is characterised by a complete lack of endogenous insulin, insulin therapy in type 2 diabetes does not completely replace, but instead supplements, the insulin still being produced by the beta-cells. How much insulin is required, and how many injections, will depend on a person's remaining endogenous insulin production capacity and the extent of the progression of the condition. Although

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people with type 2 diabetes still produce some insulin, compared with people with type 1 diabetes, bigger doses of exogenous insulin are often required, as obesity and insulin resistance are common.

Insulin regimens in type 2 diabetes vary from a single daily injection of insulin in combination with OADs to multiple injection regimens that may involve four or more injections. In contrast, in type 1 diabetes, a multiple injection regimen or insulin pump therapy is usually used to mimic the physiological insulin profile of someone without diabetes.

Insulin therapy is supported by a number of outcome studies in type 2 diabetes (Ohkubo et al, 1995; UKPDS Group, 1998) and is the only blood glucose lowering therapy for which there is no maximum dose or limit to efficacy (Nathan et al, 2006). Recent data from studies such as ACCORD (Action to Control Cardiovascular Disease in Diabetes; Gerstein et al, 2008) and the VADT (Veterans Affairs Diabetes Trial; Duckworth et al, 2009) have raised some concerns among healthcare professionals regarding the possible dangers of intensive glucose lowering in people with type 2 diabetes, and in many areas of the UK, primary care teams will be involved in the initiation and intensification of insulin therapy for people with type 2 diabetes in an effort to tighten glycaemic control, particularly given the recent adjustment of the lowest Quality and Outcomes Framework HbA_{1c} indicator.

An understanding of the different types of insulin, the various insulin regimens and whether or not OAD therapy should be adjusted is therefore important. These topics are discussed in this module. Issues specific to insulin therapy in the management of type 1 diabetes will be covered in a subsequent module.

History

Insulin is the oldest of the currently available medications for glycaemic control, with the most clinical experience. Its discovery in 1921 at the University of Toronto, Canada, led to the award of the Nobel Prize in Physiology or Medicine in 1923 for Frederick Banting and J Macleod, who shared the prize with Charles Best and James Collip. The famous experiment to "cure" diabetes with "isletin" in Marjorie the dog (who had her pancreas removed to induce diabetes) led Collip to comment:

> *"We have obtained from the pancreas of animals a mysterious something which when injected into totally diabetic dogs completely removes all the cardinal symptoms of the disease … If the substance works on the human, it will be a great boon to Medicine" (Bliss, 1982).*

The therapeutic use of insulin began with the treatment of a 14-year-old boy called Leonard Thompson in January 1922 (Bliss, 1982), and its role in the management of hyperglycaemia in type 1 diabetes is undisputed.

Insulin has also been used in the treatment of type 2 diabetes since the 1930s (Himsworth and Kerr, 1939). Indeed, until the 1940s, insulin was the only treatment available for both types of diabetes, at which point OADs were introduced in the form of the first generation of sulphonylureas. Metformin use followed in the late 1950s. The introduction of other OADs has meant that the role of insulin therapy in type 2 diabetes is less ubiquitous than in type 1 diabetes.

Mode of action

Insulin is a 51-amino acid polypeptide hormone that has an extensive and fundamental role in metabolism. It is

Box 1. Insulin therapy in type 2 diabetes: key facts and practical considerations.

- Offers rapid lowering of blood glucose levels and an improved lipid profile (Nathan et al, 2006).
- Typically reduces HbA_{1c} levels by 1.5–3.5% (17–38 mmol/mol) (Nathan et al, 2006).
- Administered by subcutaneous injection.
- Multiple regimens of varying complexity, involving between one and four or more daily injections.
- Associated with weight gain and hypoglycaemia.
- Requires self-monitoring of blood glucose levels.

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1. Insulin promotes the uptake of glucose by the liver, muscle and adipose tissue, and stimulates the storage of glucose as glycogen in the liver and muscle.
2. Hypoglycaemia is a contraindication for many insulin preparations, and is also an important side-effect.
3. Many people do gain weight when starting insulin, which is a significant issue for people with type 2 diabetes as many are already overweight.
4. Insulin preparations differ in terms of their origin and their time–action profiles.

secreted from pancreatic beta-cells in response to increases in blood glucose levels arising from the ingestion of carbohydrate-containing food, and has a number of effects on glucose homeostasis. A detailed description of all its physiological effects is beyond the scope of this article, but, notably, insulin promotes the uptake of glucose by the liver, muscle and adipose tissue, and stimulates the storage of glucose as glycogen in the liver and muscle.

As insulin is inactivated by gut enzymes, it is not suitable for oral administration, and is given by subcutaneous injection in most circumstances. Since the introduction of insulin therapy in the 1920s, a number of types of insulin preparation with different pharmacodynamic properties have been developed. These are considered in more detail in the "Types of insulin" section.

Indications and licence

While the exact wording of the therapeutic indications of different insulins varies slightly, broadly speaking, the different insulin preparations are indicated for the treatment of diabetes where insulin is required for glucose homeostasis. Some insulins, particularly the newer ones, are indicated for treatment in people above a certain age only.

Contraindications and side-effects

Hypoglycaemia is a contraindication for many insulin preparations, and is also an important side-effect. Although less common than in people with type 1 diabetes, it is still a problem with insulin therapy in type 2 diabetes, especially in older people, in whom the symptoms may not be recognised. Hypoglycaemia risk increases with the duration of insulin treatment (Zammitt and Frier, 2005), and in the UKPDS, at least one severe hypoglycaemic episode per year occurred in 2.3% of recipients (UKPDS Group, 1998).

Many people gain weight when starting insulin (Nathan et al, 2006), which is a significant issue for people with type 2 diabetes as many are already overweight. In the UKPDS, insulin therapy was associated with an average weight gain of 4 kg (UKPDS Group, 1998). This leads to increased cardiovascular risk (Russell-Jones and Khan, 2007) and can reduce adherence with treatment. A care plan and education when initiating insulin are essential to minimise the risks of weight gain and hypoglycaemia.

Types of insulin

Insulin preparations differ in terms of:

- Their origin. The amino acid sequences of animal insulins, human insulins and human insulin analogues are different. "Insulin analogues" are so called because their amino acid sequences are different from those occurring in nature, yet they retain the ability to interact with the human insulin receptor. Different techniques are also used to produce different insulin preparations. Human insulin, for example, may be generated by recombinant DNA technology using yeast or bacteria, or by enzymatic modification of porcine insulin (BMJ Group and RPS Publishing, 2009).
- Their time–action profiles. In prescribing resources, such as the *British National Formulary (BNF)* and *MIMS,* insulin preparations are typically categorised according to their time–action profiles. The categorisation in these resources differs slightly. For example, pre-mixed insulins aside, while the *BNF* (BMJ Group and RPS Publishing, 2009) considers short-acting and intermediate- and long-acting insulins, *MIMS* (Haymarket Medical, 2009) divides the preparations into very rapidly, short-, intermediate- and long-acting insulins. This article also categorises the different insulin preparations on the basis of their time–action profiles.

There are four manufacturers supplying insulin in the UK. Eli Lilly and Company Limited (Basingstoke), Novo Nordisk Limited (Crawley) and sanofi-aventis (Guildford) manufacture a variety of genetically engineered human insulin and human insulin analogues. Wockhardt UK Limited (Wrexham) is now the only supplier of animal (pork and beef) insulins.

Short- and rapid-acting insulins

Short- and rapid-acting insulins mimic the short burst of insulin associated with eating carbohydrate-containing meals produced by individuals without diabetes. They are usually injected with meals (and are therefore known also as prandial insulins), but additionally are useful in managing hyperglycaemia during periods of illness. As the name suggests, they are relatively short acting, and are usually used in combination with an intermediate- or long-acting insulin. They can be further sub-divided into short-acting (or soluble) insulins and the more recently available rapid-acting insulin analogues.

Short-acting (soluble) insulins

Soluble insulins are clear solutions that are injected between 15 and 30 minutes before meals, have a rapid onset of action (approximately 30–60 minutes), a peak action between 2 and 4 hours and can last for up to approximately 8 hours. *Figure 1* lists the soluble insulin preparations currently available in the UK.

Rapid-acting insulin analogues

Rapid-acting insulin analogues have been developed using genetic and protein engineering techniques, with the aim of changing the amino acid sequence of the human insulin molecule to reduce its tendency to self-associate (Williams and Pickup, 2004). Such changes give these preparations a faster onset of action and a shorter duration, allowing them to be injected immediately before or even after a meal, which may be more convenient for users.

There is evidence that, compared with soluble insulins, they are associated with a lower risk of hypoglycaemia (Zammitt and Frier, 2005) and can lower 2-hour postprandial blood glucose levels, lower the risk of late postprandial hypoglycaemia, and give a better quality of life through greater flexibility in timing and dosing of insulin (Rossetti et al, 2008). The currently available rapid-acting insulin analogues are listed in *Figure 1*.

Intermediate- and long-acting insulins

Intermediate- and long-acting insulins are also called basal insulins as their function is to provide a relatively steady supply of insulin to maintain blood glucose levels overnight and between meals, mimicking the background insulin produced by individuals without diabetes. Collectively, they have an onset of action within approximately 1–2 hours and a duration of between around 16 and 35 hours (BMJ Group and RPS Publishing, 2009). A number of different methods of prolonging the effect of insulin after injection have been developed over the years, including suspending human insulin with protamine or zinc and altering the amino acid sequence of human insulin.

Depending on the insulin used, they are usually given once or twice daily; before breakfast, at bedtime or both; and often in combination with OADs or short- or rapid-acting insulins. There are a number of types of intermediate- and long-acting insulin.

NPH (isophane) insulins

Isophane insulins are the "traditional" cloudy insulins, which comprise a suspension of insulin with protamine. They are commonly classified as intermediate-acting insulins and are also known as neutral protamine Hagedorn (NPH) insulin. NPH insulin must be re-suspended before use, has quite a marked peak–action profile and there may be large day-to-day variability in absorption after injection (Yki-Jarvinen, 2004), which, compared with long-acting insulin analogues, may result in variability in blood glucose levels and a higher risk of hypoglycaemia.

Information on the five NPH insulins available in the UK (Humulin I, Hypurin Bovine Isophane, Hypurin Porcine Isophane, Insulatard and Insuman Basal) is provided in *Figure 1*.

Long-acting insulin analogues

The long-acting insulin analogues are formed by alteration of the amino acid sequence of human insulin to give the desired prolonged duration of action. These preparations are clear and do not require re-suspension before use. HbA_{1c} attainment is similar to that achieved with NPH insulins, but long-acting insulin analogues may have some advantages in that their use can result in comparatively reduced

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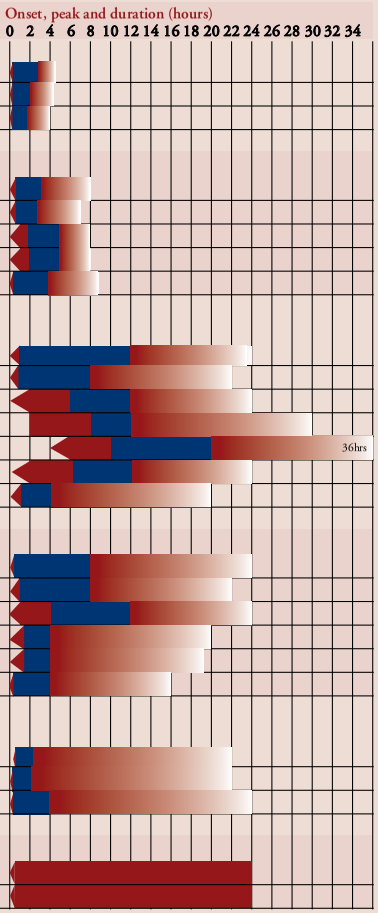
1. There are four manufacturers supplying insulin in the UK.
2. Short- and rapid-acting insulins mimic the short burst of insulin associated with eating carbohydrate-containing meals produced by individuals without diabetes.
3. Intermediate- and long-acting insulins are also called basal insulins as their function is to provide a relatively steady supply of insulin to maintain blood glucose levels overnight and between meals, mimicking the background insulin produced by individuals without diabetes.

Name	Manufacturer	Source	Delivery system	Taken
RAPID-ACTING ANALOGUE				
NovoRapid	Novo Nordisk	Analogue	Vial, cartridge, prefilled pen	Just before / with / just after food
Humalog	Lilly	Analogue	Vial, cartridge, prefilled pen (two types)	Just before / with / just after food
Apidra	sanofi-aventis	Analogue	Vial, cartridge, prefilled pen	0–15 min before, or soon after a meal
SHORT-ACTING INSULINS/NEUTRAL INSULIN				
Actrapid	Novo Nordisk	Human	Vial	30 min before food
Humulin S	Lilly	Human	Vial, cartridge	20–45 min before food
Hypurin Bovine Neutral	Wockhardt UK	Bovine	Vial, cartridge	30 min before food
Hypurin Porcine Neutral	Wockhardt UK	Porcine	Vial, cartridge	30 min before food
Insuman Rapid	sanofi-aventis	Human	Cartridge, prefilled pen	15–20 min before food
MEDIUM- AND LONG-ACTING INSULINS				
Insulatard	Novo Nordisk	Human	Vial, cartridge, pre-filled insulin doser	About 30 min before food or bed
Humulin I	Lilly	Human	Vial, cartridge, prefilled pen	About 30 min before food or bed
Hypurin Bovine Isophane	Wockhardt UK	Bovine	Vial, cartridge	As advised by your healthcare team
Hypurin Bovine Lente	Wockhardt UK	Bovine	Vial	As advised by your healthcare team
Hypurin Bovine PZI	Wockhardt UK	Bovine	Vial	As advised by your healthcare team
Hypurin Porcine Isophane	Wockhardt UK	Porcine	Vial, cartridge	As advised by your healthcare team
Insuman Basal	sanofi-aventis	Human	Vial, cartridge, prefilled pen	45–60 min before food
MIXED INSULINS				
Mixtard 30	Novo Nordisk	Human	Vial, cartridge, pre-filled insulin doser	30 min before food
Humulin M3	Lilly	Human	Vial, cartridge, prefilled pen	20–45 min before food
Hypurin Porcine 30/70 Mix	Wockhardt UK	Porcine	Vial, cartridge	As advised by your healthcare team
Insuman Comb 15	sanofi-aventis	Human	Prefilled pen	30–60 min before food
Insuman Comb 25	sanofi-aventis	Human	Vial, cartridge, prefilled pen	30–45 min before food
Insuman Comb 50	sanofi-aventis	Human	Cartridge, prefilled pen	20–30 min before food
ANALOGUE MIXTURE				
Humalog Mix 25	Lilly	Analogue	Cartridge, prefilled pen (two types)	Just before / with / just after food
Humalog Mix 50	Lilly	Analogue	Cartridge, prefilled pen (two types)	Just before / with / just after food
NovoMix 30	Novo Nordisk	Analogue	Cartridge, prefilled pen	Just before / with / just after food
LONG-ACTING ANALOGUE				
Lantus	sanofi-aventis	Analogue	Vial, cartridge, prefilled pen	Once a day, anytime (but at same time each day)
Levemir	Novo Nordisk	Analogue	Cartridge, prefilled pen, pre-filled insulin doser	Once or twice daily



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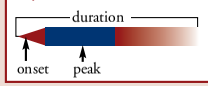

Times are approximate and may vary from person to person. This is a guide only.

Figure 1. Table of insulins available in the UK. Originally created by Diabetes UK based on information provided by insulin manufacturers. Information was correct to Diabetes UK's knowledge at the time of original publication in Spring 2009. Adapted here with kind permission of Diabetes UK. Categorisation of the insulins differs slightly from that used in the main body of this article.

fasting blood glucose levels with a lower risk of nocturnal hypoglycaemia and lower variability of blood glucose levels (Rossetti et al, 2008). However, they are more expensive than NPH.

There is evidence to suggest that treatment with insulin detemir is associated with slightly less weight gain than insulin glargine or NPH insulin (Haak et al, 2005; Dornhorst et al, 2007; Rosenstock et al, 2008), but otherwise use of the long-acting insulin analogues results in similar HbA_{1c} levels and risk of hypoglycaemia (Rosenstock et al, 2008).

They are often injected at bedtime but can be given first thing in the morning (Standl et al, 2006), and where required, insulin detemir can be given in two daily doses depending on the person's needs. There is some evidence that insulin glargine given in the morning may be more effective in reducing HbA_{1c} than that administered at bedtime (Fritsche et al, 2003).

Other preparations

Long-acting suspensions of animal insulins with zinc or protamine and zinc are also in use. Currently, two bovine preparations, Hypurin Bovine Lente and Hypurin Bovine PZI, are available in the UK (*Figure 1*).

Pre-mixed (biphasic) insulins:

As the name suggests, pre-mixed (biphasic) insulins are a mixture of a short-acting insulin or rapid-acting insulin analogue with a longer-acting protaminated version of the same insulin in a fixed ratio. The number in the name denotes the proportion of short-acting insulin in the mixture (*Figure 1*). These insulins are designed to provide a peak of activity to address postprandial hyperglycaemia, as well as a basal component to address hyperglycaemia between meals or overnight in a single injection.

The insulin appears cloudy and needs to be thoroughly re-suspended before each injection. They are usually given twice a day, before breakfast and before the evening meal, but can be given once or three times daily, with a meal (Kilo et al, 2003). Mixtures containing soluble insulin should ideally be given 15–30 minutes before the meal.

In contrast, pre-mixed insulins containing a rapid-acting insulin analogue can be given just before a meal and so may be more convenient to use than human mixtures (Garber et al, 2007). Pre-mixed insulin analogues are, however, more expensive than their human or animal counterparts.

The aim of insulin therapy in type 2 diabetes

The philosophy of insulin therapy for people with type 1 diabetes, who do not produce any insulin, is to mimic as closely as possible with exogenous insulin the insulin secretion pattern of someone who does not have diabetes. This includes a continuous, steady flow of insulin (basal) with rapid bursts of insulin (bolus) following carbohydrate consumption. Multiple injection regimens (one or two injections of intermediate- or long-acting insulin, and short- or rapid-acting insulin with meals) or insulin pumps are used to achieve this.

However, insulin therapy in type 2 diabetes is not as straightforward and there are a variety of insulin regimens in use in clinical practice. Adding insulin to type 2 diabetes treatment can significantly improve glycaemic control (Wright et al, 2002), but when and how to do so is the subject of considerable debate.

When to initiate insulin therapy in type 2 diabetes?

Evidence of the long-term benefits of achieving tight glycaemic control in the early stages of type 2 diabetes (the "legacy effect") may encourage early use of insulin (Holman et al, 2008). This is endorsed in the American Diabetes Association (ADA) and European Association of the Study of Diabetes (EASD) consensus guidelines, where insulin may be considered as a second-line add-on therapy after metformin has failed (Nathan et al, 2009).

However, NICE, in its revised type 2 diabetes guidelines (National Collaborating Centre for Chronic Conditions [NCCCC], 2008), positioned it as a third-line treatment option for most people. Similarly, the recently published update on newer therapies for blood glucose lowering in type 2 diabetes

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2. Insulin therapy in type 2 diabetes is not as straightforward as it is in type 1 diabetes and there are a variety of insulin regimens in use in clinical practice.
3. Evidence of the long-term benefits of achieving tight glycaemic control in the early stages of type 2 diabetes (the "legacy effect") may encourage early use of insulin.
4. The recently published NICE update on newer therapies for blood glucose lowering in type 2 diabetes positioned insulin as a third-line therapy option.

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1. In practice, the degree of hyperglycaemic symptoms, especially unintentional weight loss, and level of HbA_{1c} will influence how quickly insulin is introduced in a person with type 2 diabetes.
2. There is currently a paucity of evidence directly comparing the different insulin regimens in people with type 2 diabetes.
3. NICE has provided guidance on how to initiate insulin therapy and some direction on subsequent intensification.

positioned insulin as a third-line therapy option (NICE, 2009).

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Types of insulin regimen: Evidence and clinical guidance

Table 2 describes a number of the insulin regimens currently used by people with type 2 diabetes in the UK. As will be discussed below, there is currently a paucity of evidence directly comparing the different insulin regimens in people with type 2 diabetes. NICE has provided guidance on how to initiate insulin therapy and some direction on subsequent intensification (NICE, 2009).

While not exhaustive, some of the notable trials examining insulin therapy regimens in type 2 diabetes are considered below.

Direct comparisons of different insulin initiation regimens

The 3-year 4T (Treating to Target in Type 2 Diabetes) study is being conducted to directly compare the effects of different insulin analogue regimens in type 2 diabetes. The 1-year interim results were published recently (Holman et al, 2007). Overall, 708 people with suboptimal HbA_{1c} levels (7.0–10.0% [53–86 mmol/mol]) who were receiving maximally tolerated doses of metformin and sulphonylurea for at least 4 months and who had not been treated with insulin were included. Participants were randomly assigned to receive either basal insulin detemir once daily (twice if required), prandial insulin aspart three-times daily with meals, or biphasic insulin aspart twice daily.

After 1 year, the mean HbA_{1c} level was 7.3% (56 mmol/mol) in the biphasic insulin aspart group, 7.2% (55 mmol/mol) in the prandial insulin aspart group and 7.6% (60 mmol/mol) in the insulin detemir group ($P<0.001$ for comparisons with the prandial and biphasic insulin groups). The number of hypoglycaemic events experienced was 12 episodes/patient/year for the prandial regimen, 5.7 for the biphasic insulin group and 2.3 for the basal group. Mean weight gain was 5.7 kg in the prandial insulin group, 4.7 kg in the biphasic insulin group and 1.9 kg in those receiving basal insulin.

There was little difference in the proportions of participants achieving target HbA_{1c} levels between all three of the regimens if the baseline HbA_{1c} was <8.5% (<69 mmol/mol). However, the basal regimen was less effective at higher baseline HbA_{1c} levels.

The latter finding is reflected in the recommendation in the NICE type 2 diabetes guidelines that a twice-daily insulin mix should be used if baseline HbA_{1c} level is >9% (>75 mmol/mol; NICE, 2009). In summary, the basal insulin regimen was less effective at reducing HbA_{1c} levels but was associated with a lower risk of hypoglycaemia and weight gain than either the biphasic or prandial insulin regimens (Holman et al, 2007).

Similar head-to-head comparisons of insulin analogue regimens include APOLLO (A Parallel Design Comparing an Oral Antidiabetic Drug Combination Therapy with Either Lantus Once Daily or Lispro at Mealtime in Type 2 Diabetes Patients Failing Oral Treatment; Bretzel et al, 2008) and DURABLE (Durability of Basal Versus Lispro Mix 75/25 Insulin Efficacy; Buse et al, 2009).

Direct comparisons of human insulin and insulin analogue regimens

The Treat-to-Target trial (Riddle et al, 2003) was conducted to compare the effects of initiating once-daily basal insulin therapy with either NPH insulin or insulin glargine in 756 overweight people with an HbA_{1c} level between 7.5 and 10% (58 and 86 mmol/mol) with one or two OADs. A simple incremental titration programme was used, aiming to achieve a fasting blood glucose level of 5.5 mmol/L. At the end of the 24-week trial, there was no difference in the HbA_{1c} levels achieved between groups (6.96% [52.6 mmol/mol] vs. 6.97% [52.7 mmol/mol]) but a higher proportion of insulin glargine recipients achieved an HbA_{1c} level of ≤7% (≤53 mmol/mol) without nocturnal hypoglycaemia compared with those receiving NPH insulin (33.2% vs. 26.7%, respectively; $P<0.05$) (Riddle et al, 2003).

Table 2. Comparison of some type 2 diabetes insulin regimens in use in the UK, based on clinical experience.

Insulin regimen	Advantages	Disadvantages
Basal only	Simple to use Easy to titrate May involve only one daily injection Less requirement to self-monitor blood glucose levels compared with some other regimens A once-daily regimen is useful if a district nurse or other third party is required to administer injections Often a useful starting point Lower risk of hypoglycaemia and weight gain compared with other initial regimens (Holman et al, 2007; Bretzel et al, 2008)	Unlikely to enable good glycaemic control in the long term as postprandial hyperglycaemia is not addressed, and thus intensification of the regimen will be required
Twice-daily pre-mixed	Offers postprandial coverage while being relatively simple to use Offers possibility of injecting different amounts of insulin in the day and night to achieve better glycaemic control Requires only two daily injections Can be intensified to a thrice-daily regimen if required, which for some people may be more suitable than a basal–bolus regimen	Insulin needs to be resuspended thoroughly at every injection time Requires fixed mealtimes and relatively stable carbohydrate intake
Basal-plus (intermediate- or long-acting basal insulin with a short- or rapid-acting insulin with the main meal)	Potential for only two daily injections Can vary mealtime injection to suit time of the main meal May form an interim step to a basal–bolus regimen, which may ultimately be required	Higher risk of weight gain than a basal-only regimen
Basal–bolus (intermediate- or long-acting basal insulin with short- or rapid-acting insulin with each meal)	Offers greatest flexibility with timing of meals and portion sizes Achievement of HbA_{1c} targets more likely than with other regimens	Four or more injections required daily Frequent self-monitoring of blood glucose required Higher risk of hypoglycaemia and weight gain than with other regimens Not suitable for some people due to the level of motivation and understanding required to alter insulin doses in response to self-monitoring of blood glucose levels.

Similar trials have been conducted to compare the safety and efficacy of insulin detemir and NPH insulin in people with type 2 diabetes suboptimally controlled on OAD therapy (e.g. Philis-Tsimikas et al, 2006).

Comparison of titration method

It can be time-consuming supporting people with diabetes to titrate their insulin to the ideal dose. The efficacy of self-titration of insulin was assessed in the ATLANTUS study, in which 4961 people with type 2 diabetes initiating basal insulin therapy were randomised either to receive weekly advice on insulin titration by a healthcare professional, or to self-titrate their own insulin dose every few days (Davies et al, 2005). At the end of the 24-week study, the self-titrators achieved a statistically significantly greater reduction in HbA_{1c} level than their counterparts (–1.22% [–13.3 mmol/mol]

vs. –1.08% [–11.8 mmol/mol], respectively; $P<0.001$) with no more severe or nocturnal hypoglycaemia or weight gain.

What does NICE recommend?

Recommendations for OADs when used in combination with insulin

It seems sensible to continue OADs that are insulin sparing (i.e. those that reduce insulin requirements) when initiating insulin therapy, and the evidence demonstrates achievement of a significantly lower HbA_{1c}, a lower injection dose requirement and less weight gain in regimens where insulin is combined with OADs compared with insulin monotherapy (Goudswaard et al, 2004).

Specifically, NICE made the following recommendations for OADs in combination with insulin in its 2008 guidance on type 2 diabetes (NCCCC, 2008):

- When starting basal insulin therapy, continue with metformin and sulphonylureas (and acarbose, if used) but review the use of sulphonylurea if hypoglycaemia occurs.
- When starting pre-mixed insulin therapy (or basal–bolus regimens), continue with metformin and sulphonylurea initially, but discontinue the latter if hypoglycaemia occurs.
- Consider combining pioglitazone with insulin therapy in a person who has previously had a marked glucose-lowering response to a thiazolidinedione, and in people on high-dose insulin therapy whose blood glucose is inadequately controlled.

Recommendations for insulin therapy

The recommendations made in NICE's 2008 document were updated in the short clinical guideline on newer agents for blood glucose control in type 2 diabetes, which was published in May 2009 (NICE, 2009). Some of the key recommendations from the new document are quoted in *Box 2* (NICE, 2009).

Regimens summary

In summary, no single regimen is the best. In practice, there is often a compromise to be struck between the achievement of HbA_{1c} targets and minimising the risk of hypoglycaemia and weight gain, and the frequency of daily injections a person is willing to accept. The chosen regimen needs to be individualised to take account of personal choice, lifestyle, job and work shifts, travel, eating habits, dependence on others for injections, age, life expectancy, visual or manual dexterity issues, the HbA_{1c} target to be achieved, complications, other comorbidities, cognitive function, weight and hypoglycaemia risk (especially in older people).

Box 2. Abbreviated NICE recommendations for insulin therapy in type 2 diabetes (NICE, 2009).

- Begin with human neutral protamine Hagedorn (NPH) insulin injected at bed-time or twice daily according to need.
- Consider, as an alternative, using a long-acting insulin analogue if:
  - The person needs assistance to inject insulin, and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily.
  - The person's lifestyle is restricted by recurrent symptomatic hypoglycaemia.
  - The person would otherwise need twice-daily NPH insulin injections in combination with OADs.
  - The person cannot use the device to inject NPH insulin.
- Consider twice-daily pre-mixed human insulin (particularly if HbA_{1c} ≥9.0% [≥75 mmol/mol]). A once-daily regimen may be an option.
- Consider pre-mixed preparations that include short-acting insulin analogues, rather than pre-mixed preparations that include short-acting human insulin preparations, if:
  - Insulin injection immediately before a meal is preferred.
  - Hypoglycaemia is a problem.
  - Blood glucose levels rise markedly after meals.
- Consider switching to a long-acting insulin analogue from NPH insulin in people:
  - Who do not reach their target HbA_{1c} because of significant hypoglycaemia.
  - Who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA_{1c} reached.
  - Who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting insulin analogue were made.
  - Who need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.
- Monitor a person on a basal insulin regimen for the need for short-acting insulin before meals (or a pre-mixed insulin preparation).
- Monitor a person who is using pre-mixed insulin once or twice daily for the need for a further injection of short-acting insulin before meals or for a change to a regimen of mealtime plus basal insulin, based on NPH insulin or long-acting insulin analogues, if blood glucose control remains inadequate.

A once-daily basal insulin regimen added to OADs is a simple starting point but, with the progression of type 2 diabetes, is unlikely to be sufficient in the long-term. A basal insulin regimen addresses fasting hyperglycaemia in particular, but the lower the HbA_{1c} level to be achieved, the more significant the management of postprandial hyperglycaemia becomes if the target is to be reached. For example, at an HbA_{1c} level of 7.3% (56 mmol/mol), postprandial hyperglycaemia accounts for about 70% of overall hyperglycaemia and fasting hyperglycaemia accounts for around 30% (Monnier et al, 2003). In contrast, if HbA_{1c} is >10.2% (>88 mmol/mol), these percentages are reversed. As a result, postprandial hyperglycaemia will need to be addressed – either in the form of short-acting or biphasic insulin with one or more meals – to achieve tighter HbA_{1c} targets, and particularly over time as endogenous insulin secretion diminishes (Barnett et al, 2003).

Given that initial insulin regimens will require intensification, the author recommends that practitioners "think ahead" when insulin therapy is initiated. For example, some older people may struggle to self-care if prescribed a basal–bolus regimen, and in such cases intensifying a basal-only regimen by adding short-acting insulin at mealtimes would not be the most sensible long-term strategy. While there is little clinical trial evidence regarding tailoring the intensification approach to individual patients, a recent consensus statement did offer some sensible and practical suggestions (Barnett et al, 2008). *Boxes 3* and *4* provide case examples that highlight some of the practical considerations related to insulin therapy in type 2 diabetes.

Insulin adjustment

In the author's view people with type 2 diabetes should ideally be encouraged to self-titrate their insulin dose to achieve target blood glucose levels without unacceptable hypoglycaemia. Indeed, the results of the ATLANTUS study demonstrated that self-titration can be more effective than titration advised by healthcare professionals (Davies et al, 2005).

People with diabetes should be encouraged to look for patterns in their blood glucose readings, and to not alter insulin doses on the basis of a single result. They should be able to identify what the problem is (i.e. readings are above or below target), when the problem is occurring (e.g. during the night) and which insulin or insulins are active when it occurs (e.g. basal or prandial). Before making an adjustment to the insulin dose, however, other potential causes should be excluded, such as poor injection technique, use of inappropriate injection sites, lipohypertrophy, exercise, dietary indiscretions and inaccurate blood glucose monitoring.

Blood glucose monitoring readings generally inform on the effect of the last insulin injection, and therefore it is this injection that

Box 3. Case example 1.

Narrative

Mrs R is an 82-year-old white Caucasian woman who has had type 2 diabetes for 9 years. She lives alone but likes to go out regularly and also has a daughter living near by who visits her a couple of times a week. Her HbA_{1c} level has been gradually increasing over the past 2 years and is now 8.7% (72 mmol/mol). Her BMI is 26 kg/m^2 and stable. She takes metformin 1 g twice daily, gliclazide 160 mg (morning) and 80 mg (evening) and rosiglitzone 4 mg daily. She checks her own blood glucose level several times a week. On questioning, Mrs R admits to feeling more tired recently and needs to get up at least twice a night to pass urine. Her daughter commented that her mum does not go out as often as she used to and is always asleep in the chair when the daughter visits.

Discussion

Mrs R has had type 2 diabetes for at least 9 years. The results of the UKPDS (UK Prospective Diabetes Study) demonstrate that the condition is progressive and eventually most people will require insulin to keep good glycaemic control. NICE guidelines for management of type 2 diabetes recommend that the target HbA_{1c} for this woman should be 7.5% (58 mmol/mol) but concerns about her age, living alone and risk of hypoglycaemia need to be taken into consideration.

She is on triple oral therapy, and maximising the doses of rosiglitazone and gliclazide are unlikely to reduce her HbA_{1c} level by the required amount. Checking her concordance with her medication is important. Her BMI is reasonable and stable, so her diet is unlikely to be the reason for her deteriorating HbA_{1c}.

Although concerns about her age and circumstances may be a reason to avoid insulin, she is symptomatic and this is affecting the quality of her life. A daily injection of a basal insulin will be relatively easy for Mrs R to administer (she is able to use a blood glucose meter), can be titrated to relieve symptoms without significantly increasing the risk of hypoglycaemia, and will be easier for a carer or district nurse to administer should Mrs R be unable to inject herself. Showing her a range of insulin devices will help to find a pen that overcomes any manual dexterity or reduced vision problems she may have.

Rosiglitazone is not licensed for use with insulin so this treatment should be stopped. The gliclazide dose may also be reduced as the insulin dose is titrated.

should be adjusted. The paragraphs that follow give some simple advice, which is adapted from the Tayside Diabetes Handbook (NHS Tayside Diabetes MCN, 2009):

- **Once-daily basal regimen.** Increase or decrease the dose if pre-breakfast readings are above or below target, respectively.
- **Twice-daily pre-mixed insulin regimen.** Increase or decrease the morning dose if the pre-lunch and pre-evening meal readings are above or below target, respectively. Increase or decrease the evening dose if the pre-bedtime and pre-breakfast readings are above or below target, respectively.
- **Basal–bolus regimen.** Increase or decrease the basal insulin dose if pre-breakfast readings are above or below target, respectively. Increase or decrease the breakfast bolus dose if pre-lunch readings are above or below target, respectively. Increase or decrease the lunch bolus dose if pre-evening meal readings are above or below target, respectively. Increase or decrease the evening bolus dose if pre-bedtime readings are above or below target, respectively.

The amount by which the dose is adjusted can vary. The experience of the clinician, symptoms, concern about hypoglycaemia, the level of involvement of the person with diabetes and existence of complications are some of the factors that will determine how quickly and by how much insulin doses are adjusted.

Box 4. Case example 2.

Narrative

Mr D is a 58-year-old man of South Asian origin who has had type 2 diabetes for about 5 years. He started a daily basal insulin 8 months ago, initially at 10 units at bedtime and has been titrating the dose by 2 units regularly to achieve a fasting blood glucose target between 4 and 6 mmol/L. He is now injecting 68 units but his pre-breakfast readings remain stubbornly at about 7 to 9 mmol/L, his weight is increasing and he feels hungry all the time. He has tested his blood glucose before bed occasionally and found it to range from 14 to 20 mmol/L.

Discussion

Although a daily basal injection is a simple starting point when initiating insulin, and seems more acceptable to people who are reluctant to use insulin, this regimen is less likely to achieve an HbA_{1c} level of 7.5% (58 mmol/mol) than more intensive insulin regimens. The titration algorithm Mr D is using, based on regular dose increases related to fasting blood glucose levels, has been demonstrated to be an effective way for people to titrate insulin doses themselves, without requiring regular clinic visits or telephone calls (Davies et al, 2005).

However, insulin users do need to vary the timing of their blood glucose tests once the pre-breakfast readings are within target or stable. If the blood glucose level is high at another time of day (commonly before bed after the main evening meal as Mr D has found) it will impact on the fasting reading. The insulin needs to be focused on the period of hyperglycaemia. Increasing the basal insulin will increase insulin levels over the whole 24-hour period, increasing the risk of hypoglycaemia at other times, increasing hunger and causing weight gain.

Mr D has several choices:

- Reduce the amount of carbohydrate he is consuming with his evening meal (or snacks while watching the television?). Although formal carbohydrate counting is not commonly used in people with type 2 diabetes, identifying these foods and recognising that large quantities will cause hyperglycaemia is important.
- Add a short-acting insulin with his evening meal (i.e. change to a basal-plus regimen). He is likely to need a reduction in his basal insulin dose as he improves his bedtime blood glucose levels.
- Change his daily basal insulin to a pre-mixed insulin and inject this before his evening meal, to give him insulin cover for the carbohydrates consumed as well as some basal cover during the night.
- Change to a twice-daily pre-mixed insulin regimen so he can have more insulin in the evening and overnight (when he has hyperglycaemia) and a smaller dose in the morning.

Insulin delivery devices

Most insulins are available in a 10 mL vial for use with a syringe (especially useful if insulin is being given by someone else to reduce risk of stick injury), 3 mL cartridges for use in durable pens, or in 3 mL disposable pens. Insulin manufacturers generally produce insulin pen devices compatible with cartridges containing their own insulin, which are not interchangeable. Needles are available in a variety of lengths, from 5 mm to 12.7 mm, and should be used once only and disposed of according to local sharps policy.

Although insulin pump therapy is used in the USA for people with type 2 diabetes, this is not recommended by NICE (2008).

Care planning and education

All people starting insulin therapy should have a care plan agreed with their healthcare professional and a programme of education to enable them to build up their skills in self-management. The latter was recommended by NICE in its 2008 guidance on type 2 diabetes (NCCCC, 2008). Such a programme will include advice on injection technique, suitable injection sites, disposal of needles,

identification, treatment and avoidance of hypoglycaemia, management of insulin during illness, diet (weight management and carbohydrate load) and insulin adjustment to achieve target HbA_{1c} levels. Knowledge should be checked at the annual diabetes review, including inspection of injection sites for signs of lipohypertrophy.

Conclusion

Insulin therapy will ultimately be required by many people with type 2 diabetes. To minimise potential delay in changing the treatment regimen later, it is important that the eventual need for insulin is discussed early after diagnosis.

In type 2 diabetes insulin therapy is initially provided to supplement endogenous insulin secretion, and hence the regimen used is less intensive than that in type 1 diabetes, where insulin is used to mimic physiological insulin secretion. However, the progressive nature of the condition often necessitates intensification of the regimen. As such, there are a number of regimens in use, using the different properties of the various insulin preparations. ■

Page points

1. A programme of care planning and education for people with type 2 diabetes upon starting insulin will include, among others, advice on injection technique, disposal of needles and identification, treatment and avoidance of hypoglycaemia.
2. Insulin therapy will ultimately be required by many people with type 2 diabetes.
3. To minimise potential delay in changing the treatment regimen later, it is important that the eventual need for insulin is discussed early after diagnosis.

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CPD module

Online CPD activity

Visit www.diabetesandprimarycare.co.uk/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learned in practice.

1. **Which of the following is an insulin analogue? Select ONE option only.**
   A. Actrapid.
   B. Humulin S.
   C. NovoRapid.
   D. Hypurin Porcine Neutral.
   E. Hypurin Bovine Neutral.

2. **Which of the following options best describes the typical duration of action of insulin glargine? Select ONE option only.**
   A. 10 hours.
   B. 16 hours.
   C. 18 hours.
   D. 20 hours.
   E. 24 hours.

3. **When considering the 4T (Treating to Target in Type 2 Diabetes) study, which of the following is untrue? Select ONE option only.**
   A. The participants in the study had type 2 diabetes.
   B. The trial compared the effects of insulin detemir, insulin aspart and biphasic insulin aspart.
   C. When the initial HbA_{1c} level was <8.5% (<69 mmol/mol) there were limited differences between the regimens in terms of target HbA_{1c} attainment.
   D. Insulin detemir was given once or twice daily, according to need.
   E. The basal insulin was more effective at higher HbA_{1c} levels.

4. **Which of the following oral agents should not ordinarily be used with insulin? Select ONE option only.**
   A. Metformin.
   B. Gliclazide.
   C. Acarbose.
   D. Pioglitazone.
   E. Rosiglitazone.

5. **When considering NICE guidance for the initiation of insulin therapy in type 2 diabetes, which one of the following is not a recommendation? Select ONE option only.**
   A. Human neutral protamine Hagedorn (NPH) insulin should be used as a first-line option.
   B. Consider twice-daily pre-mixed human insulin, particularly for those whose HbA_{1c} is ≥9% (≥75 mmol/mol).
   C. Consider human pre-mixed insulin rather than pre-mixed preparations that include a short-acting insulin analogue if insulin injection immediately before a meal is preferred.
   D. A long-acting insulin analogue may be considered if a person's lifestyle is restricted by recurrent symptomatic hypoglycaemia.
   E. A long-acting insulin analogue may be considered if a person would otherwise need twice-daily NPH insulin injections in combination with oral antidiabetes drug therapy.

6. **When considering the ATLANTUS study, which of the following is true? Select ONE option only.**
   A. It examined pre-mixed insulin initiation, comparing the effects of self-titration and healthcare professional-led titration of doses.
   B. It examined basal insulin initiation, comparing the effects of two different self-titration algorithms.
   C. The self-titrators experienced a smaller reduction in HbA_{1c} levels than the healthcare professional-led group.
   D. The self-titrators experienced a greater improvement in glycaemic control than the healthcare professional-led group.
   E. The self-titrators experienced more severe hypoglycaemia than those in the healthcare professional-led group.

7. **A 71-year-old man who has had type 2 diabetes for 13 years attends your surgery for his annual review. He is on the maximum dose of sulphonylurea and metformin. His BMI is 31 kg/m^2, and his HbA_{1c} is 7.7% (68 mmol/mol). He has recently begun treatment with once-daily NPH insulin at bedtime, but has complained of waking up sweating and confused. Which one of the following, based on NICE's guidance on insulin therapy, would you recommend as the most appropriate next management step? Select ONE option only.**
   A. Review and possibly discontinue his sulphonylurea.
   B. Switch his NPH insulin for a premixed insulin preparation.
   C. Switch his insulin to exenatide.
   D. Review and possibly discontinue his metformin.
   E. Recommend that he inject his NPH insulin in the morning instead of at bedtime.

8. **A 78-year-old woman with a 10-year history of type 2 diabetes is due her scheduled diabetes review. She has been on a regimen of maximal metformin, sulphonylurea and thiazolidinedione for the past 2 years. Her most recent HbA_{1c} value, which is to be discussed today, is 9.5% (80 mmol/mol), and her current BMI is 28 kg/m^2. In previous consultations she was accepting that she may need insulin therapy in the future, and today you find that she leads a fixed lifestyle, with regular mealtimes. What would you advise her to do? Select ONE option only.**
   A. Initiate basal insulin therapy.
   B. Inititate exenatide therapy.
   C. Initiate a basal–bolus insulin regimen.
   D. Initiate a pre-mixed insulin regimen.
   E. Initiate a DPP-4 inhibitor.

9. **A 56-year-old man with an 8-year history of type 2 diabetes is currently on a regimen of twice-daily human NPH in combination with a fixed-dose combination of metformin 1700 mg and pioglitazone 30 mg daily. He did not tolerate sulphonylurea therapy when it was trialled as an add-on to metformin 4 years ago. He has a busy and somewhat erratic lifestyle, with variable mealtimes and often-differing portion sizes, but remains motivated in his approach to self-management. Given that his current HbA_{1c} level is 8.3% (67 mmol/mol), having deteriorated appreciably since his last review, and assuming that he has titrated his NPH dose sensibly over time, what would you suggest as a next step? Select ONE option only.**
   A. Switch NPH insulin to exenatide.
   B. Initiate sulphonylurea therapy.
   C. Switch his NPH insulin to a twice-daily premixed insulin preparation.
   D. Continue to increase his NPH insulin dose.
   E. Add short- or rapid-acting insulin at mealtimes as part of a basal–bolus regimen.

10. **A 75-year-old man with Alzheimer's disease and a 12-year history of type 2 diabetes has until now managed his blood glucose levels with a regimen of maximal doses of metformin, sulphonylurea and a thiazolidinedione. You prescribed bedtime NPH insulin 6 months ago. Currently, he has an HbA_{1c} level of 8.8% (73 mmol/mol) and is a nursing home resident. He is unable to adequately self-care, and requires the care home staff to assist him in managing his diabetes. Based on blood glucose monitoring results you decide that he would benefit from a second daily dose of NPH insulin. According to NICE's recommendations, which would be the most suitable next management step? Select ONE option only.**
    A. Intensify the regimen to basal–bolus.
    B. Switch him to a once-daily long-acting insulin analogue.
    C. Add a second daily injection of human NPH insulin.
    D. Switch him to a twice-daily human pre-mixed insulin preparation.
    E. Switch him to a twice-daily pre-mixed preparation containing a rapid-acting insulin analogue.