



# UNIT 1 Core aspects of care

## Insulin therapy in type 2 diabetes

### Online learning

Visit [diabetesonthenet.com/cpd](http://diabetesonthenet.com/cpd) to gain a certificate of continuing professional development for participating in this module.

See page 261

**Citation:** Hill J (2015) Insulin therapy in type 2 diabetes. *Diabetes & Primary Care* 17: 252–61

### 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.
4. Be aware of new insulin preparations and their clinical implications.

### Key words

- Hypoglycaemia
- Insulin
- Insulin regimens
- Weight gain

### Author

Jill Hill is a Diabetes Specialist Nurse, Shropshire Community Health NHS Trust, and Co-Chair of TREND-UK.

### Jill Hill

**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 module covers the different types of insulin and insulin regimen currently in use in the UK for people with type 2 diabetes, summarises current clinical guidance and raises awareness about potential safety issues.**

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 deterioration in glycaemic control evidenced by an increase in HbA<sub>1c</sub> (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<sub>1c</sub> level (Turner et al, 1999). 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 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, weight gain and driving implications, 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 people with type 2 diabetes still produce some insulin, compared with people with type 1 diabetes, bigger

**Supported by an educational grant from Janssen, part of the Johnson & Johnson Family of Diabetes Companies. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with Diabetes & Primary Care. The sponsor had no input into the module and is not responsible for its content.**

Supported by an educational grant from Janssen, part of the Johnson & Johnson Family of Diabetes Companies. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with *Diabetes & Primary Care*. The sponsor had no input into the module and is not responsible for its content.

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 daily 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 current blood glucose-lowering therapy for which there is no maximum dose or limit to efficacy (Inzucchi et al, 2015). More recent data from studies such as the ACCORD (Action to Control Cardiovascular Disease in Diabetes) study (Gerstein et al, 2008) and VADT (the 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 long-standing type 2 diabetes.

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. An understanding of the different types of insulin, the various insulin regimens, and whether or not OAD therapy should be adjusted is therefore important.

### Mode of action

Insulin is a 51-amino acid polypeptide hormone that has an extensive and fundamental role in metabolism. It is secreted from pancreatic beta-cells in response to increases in blood glucose levels arising from the ingestion of carbohydrate-containing food, and it 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 it 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

### 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, 2009)
- Typically reduces HbA<sub>1c</sub> levels by 17–38 mmol/mol (1.5–3.5 percentage points; Nathan et al, 2009)
- 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

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, the different insulin preparations, broadly speaking, 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 (UK Hypoglycaemia Study Group, 2007), especially in older people, in whom the symptoms may not be recognised. Hypoglycaemia risk increases with the duration of insulin treatment (Zammit 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 (Inzucchi et al, 2015), 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 to treatment. A

Supported by an educational grant from Janssen, part of the Johnson & Johnson Family of Diabetes Companies. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with *Diabetes & Primary Care*. The sponsor had no input into the module and is not responsible for its content.

### Page points

1. Short- and rapid-acting insulins mimic the short burst of insulin associated with eating carbohydrate-containing meals produced by individuals without diabetes.
2. 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.

care plan and education when initiating insulin are essential to minimise the risks of weight gain and hypoglycaemia.

Other safety-related issues relevant to insulin use in type 2 diabetes that have arisen more recently are covered later in this module in their own section.

### 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.
- **Their time–action profiles.**

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

A chart showing key properties of different types of insulin can be found in the previous version of this module (Hill, 2012; <http://bit.ly/1JuSerq>). Since the publication of that chart, the new long-acting insulin Tresiba® (insulin degludec; Novo Nordisk) has been launched. This analogue insulin is available in a cartridge and in a pre-filled device, has a duration of action beyond 42 hours and is manufactured in strengths of 100 units/mL (electronic Medicines Compendium [eMC], 2015d) and 200 units/mL (eMC, 2015e). Also now available is Toujeo®, a 300-units/mL strength preparation of insulin glargine (Sanofi) in a pre-filled device (eMC, 2015c). Finally, the first biosimilar insulin, Abasaglar® (insulin glargine; Eli Lilly and Company) has recently been launched. Abasaglar, Toujeo and Tresiba are discussed further in the “Long-acting insulin analogues” section.

### 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 they are also useful in managing hyperglycaemia during periods of illness. They are relatively short acting and are usually used in combination with an intermediate- or long-acting insulin. (For more details, see Hill [2012; <http://bit.ly/1JuSerq>].)

#### Short-acting (soluble/neutral) insulins

Soluble insulins are clear solutions that are injected approximately 15–30 minutes before meals, have a rapid onset of action (approximately 30–60 minutes), have a peak action between approximately 2 and 4 hours and can last for up to around 8 hours.

#### 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 (Zammit 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).

### 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 of approximately 30 minutes to 2 hours and a duration of between around 16 and 42 hours. A number of different methods of prolonging the effect of insulin after injection have been developed

Supported by an educational grant from Janssen, part of the Johnson & Johnson Family of Diabetes Companies. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with *Diabetes & Primary Care*. The sponsor had no input into the module and is not responsible for its content.

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. (For more details, see Hill [2012; <http://bit.ly/1JuSerq>].)

### 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, it has quite a marked peak in its time–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 (Rossetti et al, 2008).

### 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<sub>1c</sub> 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 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 insulins.

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 use of the long-acting insulin analogues results in similar HbA<sub>1c</sub> 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<sub>1c</sub> than that administered at bedtime (Fritsche et al, 2003).

Tresiba (insulin degludec) has an action profile extending beyond 42 hours. It is still recommended that it be given once daily, but the extended action profile is useful for people who find it difficult to give their background insulin at a regular time. As mentioned earlier, it is available in strengths of 100 units/mL – in cartridges and FlexTouch® pre-filled device pens (eMC, 2015d) – and 200 units/mL – in FlexTouch pens only (eMC 2015e). The 200 units/mL formulation is useful for people requiring large doses of insulin (and therefore needing to inject a relatively large volume of fluid subcutaneously) as the pen devices can deliver 160 units of insulin in half the volume that would be given using the 100 units/mL strength.

Toujeo (300 units/mL of insulin glargine) is also now available, in disposable SoloStar® pen devices (eMC, 2015c).

### Biosimilars

Abasaglar is a biosimilar preparation of insulin glargine and is available in 3-mL cartridges for use in Eli Lilly and Company re-usable devices and the disposable KwikPen™ (eMC, 2015a). For more information on biosimilar medicinal products, see <http://bit.ly/1PCppri>.

### Other preparations

Long-acting suspensions of animal insulins with zinc, or protamine and zinc, are also in use.

### 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 brand name denotes the proportion of short-acting insulin in the mixture. 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

### Page points

1. 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.
2. 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.
3. 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.

Supported by an educational grant from Janssen, part of the Johnson & Johnson Family of Diabetes Companies. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with Diabetes & Primary Care. The sponsor had no input into the module and is not responsible for its content.

### Page points

1. A once-daily basal insulin regimen added to oral antidiabetes drugs is a simple starting point but, with the progression of type 2 diabetes, is unlikely to be sufficient in the long term.
2. A basal insulin regimen addresses fasting hyperglycaemia in particular, but the lower the HbA<sub>1c</sub> level to be achieved, the more significant the management of postprandial hyperglycaemia becomes if the target is to be reached.

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.

### Insulins in combination therapies

As obesity is present in most people with type 2 diabetes, glucagon-like peptide-1 (GLP-1) receptor agonist therapy may be first injection treatment of choice, which can delay the initiation of insulin. This class of medication may give the benefit of weight reduction as well as a reduction in HbA<sub>1c</sub>. Insulin is often required to maintain glycaemic control, but most GLP-1 receptor agonists can be used in combination with insulin therapy (the exception being the extended-release preparation of exenatide, Bydureon® [eMC, 2015b]), where the former treatment shows clinical benefit. The recent availability of the GLP-1 receptor agonist liraglutide in combination with insulin degludec allows people to have a single daily injection (Xultophy®; Novo Nordisk) with two modes of action. Xultophy has a specific dosing schedule and is measured in steps rather than units. Each “step” contains 1 unit of insulin degludec and 0.036 mg of liraglutide. The starting dose is 16 steps, with 50 steps being the maximum dose (containing 50 units of insulin degludec and 1.8 mg of liraglutide; eMC, 2015f).

### 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.

### Choice of insulin regimen

Table 1 describes a number of the insulin regimens currently used by people with type 2 diabetes in the UK. No single regimen is the best. In practice, there is often a compromise to be struck between the achievement of HbA<sub>1c</sub> 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<sub>1c</sub> target to be achieved, complications, other comorbidities, cognitive function, weight and hypoglycaemia risk (especially in older people).

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<sub>1c</sub> 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<sub>1c</sub> level of 56 mmol/mol (7.3%), postprandial hyperglycaemia accounts for about 70% of overall hyperglycaemia and fasting hyperglycaemia accounts for around 30% (Monnier et al, 2003). In contrast, if HbA<sub>1c</sub> is >88 mmol/mol (>10.2%), these percentages are reversed. As a result, postprandial hyperglycaemia will need to be addressed – in the form of either short-acting or biphasic insulin with one or more meals – to achieve tighter HbA<sub>1c</sub> targets, 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

Supported by an educational grant from Janssen, part of the Johnson & Johnson Family of Diabetes Companies. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with Diabetes & Primary Care. The sponsor had no input into the module and is not responsible for its content.

regimen by adding short-acting insulin at meal-times would not be the most sensible long-term strategy. A consensus statement from 2008 offers some sensible and practical suggestions in this area (Barnett et al, 2008).

Some of the notable trials examining insulin therapy regimens in type 2 diabetes are described in previous versions of this module (Hill, 2009; 2012 [<http://bit.ly/1JuSerq>]). At the time of writing, the publication of the updated NICE guideline on type 2 diabetes is imminent. Readers are advised to refer to this guideline once published.

### When should we 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 and

European Association for the Study of Diabetes consensus guidelines, where insulin is considered as an option for second-line add-on therapy after metformin has failed (Inzucchi et al, 2015). However, NICE (2009), in its guideline on newer therapies for blood glucose lowering in type 2 diabetes, positioned insulin as a third-line therapy option. This seems unlikely to change in the revised guideline.

In practice, the degree of hyperglycaemic symptoms, especially unintentional weight loss, and level of HbA<sub>1c</sub> will influence how quickly insulin is introduced in a person with type 2 diabetes.

### Starting and adjusting insulin

#### Start doses

Guidance from the Royal College of Nursing (2012) on “Starting insulin treatment in adults with Type 2 diabetes” makes the following comment concerning start doses:

**Table 1. Comparison of some type 2 diabetes insulin regimens in use in the UK, based on the author’s clinical experience.**

Insulin regimen	Advantages	Disadvantages
<b>Basal only</b>	<ul style="list-style-type: none"> <li>Simple to use</li> <li>Easy to titrate</li> <li>May involve only one daily injection</li> <li>Less requirement to self-monitor blood glucose levels compared with some other regimens</li> <li>A once-daily regimen is useful if a district nurse or other third party is required to administer injections</li> <li>Often a useful starting point</li> <li>Lower risk of hypoglycaemia and weight gain compared with other initial regimens (Bretzel et al, 2008; Holman et al, 2009)</li> </ul>	<ul style="list-style-type: none"> <li>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</li> </ul>
<b>Twice-daily pre-mixed</b>	<ul style="list-style-type: none"> <li>Offers postprandial coverage while being relatively simple to use</li> <li>Offers possibility of injecting different amounts of insulin in the day and night to achieve better glycaemic control</li> <li>Requires only two daily injections</li> <li>Can be intensified to a thrice-daily regimen if required, which for some people may be more suitable than a basal-bolus regimen</li> </ul>	<ul style="list-style-type: none"> <li>Insulin needs to be resuspended thoroughly at every injection time</li> <li>Requires fixed meal-times and relatively stable carbohydrate intake</li> </ul>
<b>Basal-plus (intermediate- or long-acting basal insulin with a short- or rapid-acting insulin with the main meal)</b>	<ul style="list-style-type: none"> <li>Potential for only two daily injections</li> <li>Can vary meal-time injection to suit time of the main meal</li> <li>May form an interim step to a basal-bolus regimen, which may ultimately be required</li> </ul>	<ul style="list-style-type: none"> <li>Higher risk of weight gain than with a basal-only regimen</li> </ul>
<b>Basal-bolus (intermediate- or long-acting basal insulin with short- or rapid-acting insulin with each meal)</b>	<ul style="list-style-type: none"> <li>Offers greatest flexibility with timing of meals and portion sizes</li> <li>Achievement of HbA<sub>1c</sub> targets more likely than with other regimens</li> </ul>	<ul style="list-style-type: none"> <li>Four or more injections required daily</li> <li>Frequent self-monitoring of blood glucose required</li> <li>Not suitable for some people owing to the level of motivation and understanding required to alter insulin doses in response to self-monitoring of blood glucose levels</li> </ul>

Supported by an educational grant from Janssen, part of the Johnson & Johnson Family of Diabetes Companies. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with Diabetes & Primary Care. The sponsor had no input into the module and is not responsible for its content.

### Page points

1. People with type 2 diabetes should ideally be encouraged to self-titrate their insulin dose to achieve target blood glucose levels without unacceptable hypoglycaemia.
2. Most insulins are available in a 10-mL vial for use with a syringe, in 3-mL cartridges for use in durable pens, or in 3-mL disposable pens.
3. Insulin manufacturers generally produce insulin pen devices compatible with cartridges containing their own insulin, which are not interchangeable.

“Once-daily regimens often start with 10 units. Most twice-daily regimens start with 6–10 units twice daily, depending upon the person’s weight. Starting low and giving clear insulin titration guidance over the following months will build the person’s confidence and your own.”

### 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 AT.LANTUS 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 provide information on the effect of the last insulin injection, and therefore it is this injection that should be adjusted. The following advice is adapted from guidance given by the Royal College of Nursing (2012):

- **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. The frequency of blood glucose monitoring will vary depending on the regimen, with the number of tests required increasing with the number of insulin doses given each day. A sufficient supply of blood glucose monitoring strips is essential for people to have enough information to titrate their insulin doses safely and effectively (TREND-UK, 2014).

### Insulin delivery devices

Most insulins are available in a 10-mL vial for use with a syringe, in 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.

A small number of individuals are unable to find a pen device to suit their needs and require the support of a community nurse yet wish to maintain independence in giving their own insulin at a time to suit them. Guidelines on preparing insulin syringes in advance are available from the Royal College of Nursing (2015).

Needles are available in a variety of lengths, from 4 mm to 12.7 mm, and they should be used once only and disposed of according to local sharps policy. Generally, the shorter needles are appropriate as there is no clinical reason for recommending needles >8 mm. If injecting into slim limbs, a small pinch up of skin is still required even with short needles, to ensure insulin is injected into sub-cutaneous fat rather than muscle (Forum for Injection Technique [FIT], 2011)

Concern about the frequency of sharps injuries associated with healthcare professionals administering insulin resulted in a European directive in 2010 that gives guidance about safe disposal of sharps and the use of safety-engineered

Supported by an educational grant from Janssen, part of the Johnson & Johnson Family of Diabetes Companies. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with *Diabetes & Primary Care*. The sponsor had no input into the module and is not responsible for its content.

needles and syringes. These devices ensure the needle is completely covered before and after the injection is given, to avoid accidental injury to the person using the device. The directive recommends that all people requiring healthcare professional administration of insulin should be prescribed safety needles. They should also be prescribed for people with conditions such as HIV and in unsafe environments where children or people with dementia, for example, could access the used needles of someone who self-administers insulin (FIT, 2012).

Although insulin pump therapy is used in the US 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 2009 guidance on type 2 diabetes (NICE, 2009). 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<sub>1c</sub> levels. Knowledge should be checked at the annual diabetes review, including inspection of injection sites for signs of lipohypertrophy. A comprehensive guide is available from the Royal College of Nursing (2012).

### Safe use of insulin

A report by the NHS's National Patient Safety Agency (NPSA) revealed that there had been over 16 000 medication incident reports involving insulin between 1 November 2003 and 1 November 2009 (NPSA, 2010; 2011). These included errors resulting from abbreviating "units" to "u" or "iu", as well as many mistakes relating to people being given the wrong insulin owing to the names of several insulins being similar. People using insulin should be given an insulin passport by the prescriber stating the name and delivery system of their insulin, and they should be advised to always check they have the correct insulin when collecting it from the pharmacy.

The availability of insulins of different strengths is a potential safety issue. Both Toujeo and the 200 unit/mL formulation of Tresiba are only available in a pre-filled device. Insulin should not be drawn out of these devices into an insulin syringe as these are for use with 100 unit/mL insulins and will therefore result in a significant overdose.

All healthcare professionals involved in the prescribing, dispensing and administration of insulin should access regular training on insulin management to reduce errors. A free e-learning package, developed by the Primary Care Diabetes Society in collaboration with TREND-UK, is available at [cpd.diabetesonthenet.com](http://cpd.diabetesonthenet.com). Nurses and unregistered practitioners should ensure they meet the competencies expected in their role regarding insulin (TREND-UK, 2015).

### Driving legislation

Changes to the Driver and Vehicle Licensing Agency (DVLA) medical standards potentially have a significant bearing on drivers with diabetes who are treated with insulin (DVLA, 2015). People using insulin should test their blood glucose level before driving, and ensure the result is above 5 mmol/L. People with insulin-treated diabetes can now apply to hold a licence to drive Group 2 vehicles (large goods vehicles and passenger-carrying vehicles) as long as they meet specific safety criteria, which include:

- Monitoring blood glucose at least twice daily, and at times relevant to driving, using a meter with a memory function.
- Attending an annual examination by a diabetologist, at which they will need to have 3 months of glucose readings available for examination.
- Having good awareness of hypoglycaemia symptoms.

Any driver who has more than one episode of severe hypoglycaemia (i.e. that requiring the help of another person) in a year, even if unrelated to driving, must inform the DVLA and will lose his or her licence (Group 2 vehicle licence drivers must report any episode). There is evidence that this may lead to insulin users not seeking help for hypoglycaemia problems because of concerns of disqualification (Pedersen-Bjergaard et al, 2014).

### Page points

1. 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.
2. A report by the NHS's National Patient Safety Agency revealed that there had been over 16 000 medication incident reports involving insulin between 1 November 2003 and 1 November 2009.
3. People using insulin should test their blood glucose level before driving, and ensure the result is above 5 mmol/L.



Supported by an educational grant from Janssen, part of the Johnson & Johnson Family of Diabetes Companies. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with Diabetes & Primary Care. The sponsor had no input into the module and is not responsible for its content.

**“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.”**

### Insulin economics

The cost-effectiveness of insulin analogues compared with human insulins has been the topic of debate in recent years. It has been argued that “for most people with type 2 diabetes the extra cost does not correspond to the equivalent extra benefit” (Cohen and Carter, 2010). As described earlier, NICE (2009) recommends a starting regimen of NPH insulin injected at bedtime or twice daily according to need, although it acknowledges that there are circumstances in which long-acting insulin analogues are still appropriate. The cost aspects of this remain a concern in 2015 (NICE, 2015).

### 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. There are a number of regimens in use, using the different properties of the various insulin preparations. ■

Barnett A et al (2003) *Practical Diabetes International* **20**: 97–102

Barnett A et al (2008) *Int J Clin Pract* **62**: 1647–53

Bretzel RG et al (2008) *Lancet* **371**: 1073–4

Cohen D, Carter P (2010) *BMJ* **341**: C7139

Davies M et al (2005) *Diabetes Care* **28**: 1282–8

Dornhorst A et al (2007) *Int J Clin Pract* **61**: 523–8

Driver and Vehicle Licensing Agency (2015) *For medical practitioners: At a glance guide to the current medical standards of fitness to drive*. DVLA, Swansea. Available at: <https://www.gov.uk/government/publications/at-a-glance> (accessed 25.08.15)

Duckworth W et al (2009) *N Engl J Med* **360**: 129–39

electronic Medicines Compendium (2015a) *ABASAGLAR 100 units/mL solution for injection in cartridge & pre-filled pen*. eMC, Leatherhead. Available at: <http://www.medicines.org.uk/emc/medicine/30494> (accessed 25.08.15)

electronic Medicines Compendium (2015b) *Bydureon 2 mg powder and solvent for prolonged-release suspension for injection in pre-filled pen*. eMC, Leatherhead. Available at: <http://www.medicines.org.uk/emc/medicine/29798> (accessed 25.08.15)

electronic Medicines Compendium (2015c) *Toujeo 300 units/ml solution for injection in a pre-filled pen*. eMC, Leatherhead. Available at: <http://www.medicines.org.uk/emc/medicine/30586> (accessed 25.08.15)

electronic Medicines Compendium (2015d) *Tresiba 100 units/mL Pre-filled Pen (FlexTouch)*. eMC, Leatherhead. Available at: <http://www.medicines.org.uk/emc/medicine/27359> (accessed 25.08.15)

electronic Medicines Compendium (2015e) *Tresiba 200 units/mL Pre-filled Pen (FlexTouch)*. eMC, Leatherhead. Available at: <http://www.medicines.org.uk/emc/medicine/27363> (accessed 25.08.15)

electronic Medicines Compendium (2015f) *Xultophy 100 units/ml insulin degludec + 3.6 mg/mL liraglutide solution for injection in a pre-filled pen*. eMC, Leatherhead. Available at: <http://www.medicines.org.uk/emc/medicine/29493> (accessed 25.08.15)

Forum for Injection Technique (2011) *The First UK Injection Technique Recommendations* (2nd edition). Available at: <http://www.fit4diabetes.com/united-kingdom/> (accessed 25.08.15)

Forum for Injection Technique (2012) *FIT4Safety Injection Safety in UK and Ireland: Safety of Sharps in Diabetes Recommendations* (1<sup>st</sup> edition). Available at: <http://www.fit4diabetes.com/united-kingdom/fit-safety-recommendations/> (accessed 25.08.15)

Fritsche A et al (2003) *Ann Intern Med* **138**: 952–9

Garber AJ et al (2007) *Diabetes Obes Metab* **9**: 630–9

Gerstein HC et al (2008) *N Engl J Med* **358**: 2545–59

Haak T et al (2005) *Diabetes Obes Metab* **7**: 56–64

Hill J (2009) *Diabetes & Primary Care* **11**: 162–74

Hill J (2012) *Diabetes & Primary Care* **14**: 163–76

Holman RR et al (2008) *N Engl J Med* **359**: 1577–89

Holman RR et al (2009) *N Engl J Med* **361**: 1736–47

Inzucchi SE et al (2015) *Diabetes Care* **38**: 140–9

Kilo C et al (2003) *J Diabetes Complications* **17**: 307–13

Monnier L et al (2003) *Diabetes Care* **26**: 881–5

Nathan DM, Buse JB, Davidson MB et al (2009) *Diabetes Care* **32**: 193–203

National Patient Safety Agency (2010) *Safer administration of insulin*. Available at: <http://www.nrls.npsa.nhs.uk/alerts/?entryid45=74287> (accessed 25.08.15)

National Patient Safety Agency (2011) *The adult patient's passport to safer use of insulin*. Available at: <http://www.nrls.npsa.nhs.uk/resources/?EntryId45=130397> (accessed 25.08.15)

NICE (2008) *Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus* (TA151). NICE, London. Available at: <https://www.nice.org.uk/Guidance/TA151> (accessed 25.08.15)

NICE (2009) *Type 2 diabetes: The management of type 2 diabetes*. (CG87). NICE, London. Available at: <http://www.nice.org.uk/guidance/cg87> (accessed 25.08.15)

NICE (2015) *Medicine management options for local implementation*. NICE, London. Available at: <http://bit.ly/1KhmxHc> (accessed 25.08.15)

Ohkubo Y et al (1995) *Diabetes Res Clin Pract* **28**: 103–17

Pedersen-Bjergaard U et al (2014) *Diabetes Care* **38**: 29–33

Rosenstock J et al (2008) *Diabetologia* **51**: 408–16

Rossetti P et al (2008) *Arch Physiol Biochem* **114**: 3–10

Royal College of Nursing (2012) *Starting injectable treatment in adults with Type 2 diabetes*. RCN, London. Available at: <http://bit.ly/18BjAu> (accessed 25.08.15)

Royal College of Nursing (2015) *Advanced preparation of insulin syringes for adult patients to administer at home*. Available at: <http://bit.ly/1JhaIGD> (accessed 25.08.15)

Russell-Jones D, Khan R (2007) *Diabetes Obes Metab* **9**: 799–812

Standl E et al (2006) *Horm Metab Res* **38**: 172–7

TREND-UK (2014) *Blood Glucose Monitoring Guidelines: Consensus Document*. Available at: <http://www.trend-uk.org/resources.php> (accessed 25.08.15)

TREND-UK (2015) *An Integrated Career and Competency Framework for Diabetes Nursing* (4<sup>th</sup> edition). Available at: <http://www.trend-uk.org/resources.php> (accessed 25.08.15)

Turner RC et al (1999) *JAMA* **281**: 2005–12

UK Hypoglycaemia Study Group (2007) *Diabetologia* **50**: 1140–7

UKPDS Group (1995) *Diabetes* **44**: 1249–58

UKPDS Group (1998) *Lancet* **352**: 837–53

Williams GM, Pickup JC (2004) *Handbook of Diabetes*. Blackwell Publishing, Oxford

Wright A et al (2002) *Diabetes Care* **25**: 330–6

Yki-Jarvinen H (2004) *Eur J Clin Invest* **34**: 410–16

Zammit NN, Frier BM (2005) *Diabetes Care* **28**: 2948–61

### Case examples

Case examples can be found in the previous version of this module:

<http://bit.ly/1JuSerq>

Supported by an educational grant from Janssen, part of the Johnson & Johnson Family of Diabetes Companies. These modules were conceived and are delivered by the Primary Care Diabetes Society in association with *Diabetes & Primary Care*. The sponsor had no input into the module and is not responsible for its content.

## Online CPD activity

Visit [www.diabetesonthenet.com/cpd](http://www.diabetesonthenet.com/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. A short explanation of the correct answer is provided. 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 learnt in practice. The CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

- In addition to insulin resistance, which of the following is also cited as an explanation for why people with type 2 diabetes require more exogenous insulin than those with type 1? Select ONE option only.
  - Age
  - Ethnicity
  - Gender
  - Height
  - Weight
- A 58-year-old man has poor control of his type 2 diabetes and is about to be switched to insulin therapy.
 

According to UKPDS data, what is the average expected weight gain (in kg) associated with insulin therapy in this situation? Select ONE option only.

  - 2
  - 4
  - 8
  - 12
  - 16
- Which GLP-1 receptor agonist is not licensed in combination with insulin? Select ONE option only.
  - Bydureon
  - Byetta
  - Lyxumia
  - Trulicity
  - Victoza
- Which is the single most appropriate insulin regimen to recommend to people with type 2 diabetes requiring insulin in addition to oral antidiabetes agents? Select ONE option only.
  - Rapid-acting insulin
  - Short-acting insulin
  - Intermediate-acting insulin
  - Long-acting insulin
  - No single regimen is best
- According to 2012 RCN guidelines, which is the most appropriate starting dose of once-daily basal insulin? Select ONE option only.
  - 2 units
  - 4 units
  - 6 units
  - 8 units
  - 10 units
- A 49-year-old man with type 2 diabetes takes metformin 1.5 g twice daily and a twice-daily pre-mixed insulin regimen. His pre-lunch and pre-evening meal blood glucose readings are regularly higher than target.
 

Which is the single most appropriate next management step? Select ONE option only.

  - Add a sulphonylurea
  - Increase morning metformin
  - Increase morning pre-mixed insulin
  - Increase evening metformin
  - Increase evening pre-mixed insulin
- A 70-year-old woman injects once-daily long-acting insulin each evening. She plans to drive on a motorway trip tomorrow morning.
 

According to 2015 DVLA guidance, which is the most appropriate advice regarding blood glucose testing in relation to her planned journey? Select ONE option only.

  - Measure blood glucose after breakfast
  - Measure blood glucose before breakfast
  - Measure blood glucose before driving
  - Measure blood glucose before going to sleep
  - Measure blood glucose one hour after injecting
- According to Nathan et al (2009), what is the typical MAXIMUM reduction in HbA<sub>1c</sub> levels to be expected when initiating insulin for a person with type 2 diabetes? Select ONE option only.
  - 20 mmol/mol
  - 35 mmol/mol
  - 50 mmol/mol
  - 65 mmol/mol
  - 80 mmol/mol
- Which of the following insulin regimens is MOST likely to achieve HbA<sub>1c</sub> targets in people with type 2 diabetes? Select ONE option only.
  - Basal-bolus
  - Basal only
  - Basal-plus
  - Twice-daily pre-mixed
- Which insulin has the LONGEST potential duration of action? Select ONE option only.
  - Humulin S
  - Hypurin Bovine PZI
  - Insuman Comb 50
  - Levemir
  - NovoMix 30