When is insulin therapy indicated for the control of blood glucose in type 2 diabetes?

In this article Elizabeth Hackett and Winston Crasto address the ever-growing problem of diabetes. They emphasise how to ascertain when insulin therapy is indicated for type 2 diabetes and how best this can be managed using a case presentation to illustrate their points. This article follows the basic pharmacy skills series style.

Introduction

The prevalence of diabetes is reaching epidemic proportions with 2.3 million in the current UK population having been diagnosed with the condition. This figure has been estimated to rise to 4.2 million by 2025.[1] Type 2 diabetes mellitus (T2DM) is characterised by insulin resistance and the progressive decline of pancreatic beta cell function. Therefore, despite escalating doses of oral glucose-lowering agents, many people with T2DM will require the introduction of insulin therapy to achieve optimal glycaemic control.

This article sets out to discuss when insulin therapy is indicated for T2DM, what insulin regimens are suitable, how to start them and what barriers patients might have to starting insulin.

The case

Mr DD is a 45-year old man who works as a delivery driver and was diagnosed with T2DM four years ago. He also has the commonly-associated conditions of hypertension and dyslipidaemia, and he is overweight. Mr DD and his GP agreed a target HbA_{1c} of less than 6.5% because he is relatively young and the evidence suggests that tighter glycaemic control is associated with fewer microvascular complications in the future.[2] Mr DD reported to his GP that he is currently experiencing tiredness, a lack of energy and he said that he has to get up at least twice each night to pass urine. Over the past 12 months Mr DD has been experiencing deteriorating glucose control and his oral glucose-lowering medications have been titrated to maximum tolerated doses, as listed below.

Mr DD's current medications include:

- ☐ Aspirin 75mg OM
- ☐ Simvastatin 40mg ON
- ☐ Ezetimibe 10mg OM
- ☐ Ramipril 10 mg OM
- ☐ Bendroflumethiazide 2.5mg OM
- ☐ Amlodipine 10mg OM
- ☐ Metformin 850mg TDS
- ☐ Gliclazide 160mg BD.

He has previously tried 'triple therapy' with pioglitazone. However, he experienced ankle swelling, which resolved on discontinuation.

Mr DD's GP asked him if he was taking his medication regularly and Mr DD assured him that he 'never misses a dose'. The GP therefore checked his blood pressure and arranged for blood tests. The following results were obtained:

- ☐ BP 128/78 mmHg
- ☐ Total cholesterol 3.7 mmol/L
- ☐ LDL 1.9 mmol/L
- ☐ Random blood glucose 12.7 mmol/L
- ☐ HbA1c 8.6%.

Mr DD was invited back to the surgery to discuss starting insulin therapy. However, he is very worried about starting insulin because his job requires him to drive a delivery van for much of the day.

Question 1: When is long-term insulin therapy indicated for the management of T2DM?

Insulin therapy for T2DM may be started at any time, but it is usually commenced when glucose control deteriorates (or persistently falls outside recommended targets) despite optimising oral therapies or when oral therapies are not tolerated. In these cases the patient may be experiencing symptoms of hyperglycaemia (such as tiredness, lethargy, polyuria, nocturia, thirst, weight loss, recurrent fungal or bacterial infections).

The National Institute for Health and Clinical Excellence (NICE) has set a general target HbA_{1c} of 6.5% for people with T2DM. However, NICE recommends that the target is individualised and agreed with the patient, and that for some a level above 6.5% may be more appropriate.[3] Furthermore, NICE advises against pursuing highly intensive management regimens of less than 6.5%.[3] This recommendation has since been endorsed by publication of the ACCORD (action to control cardiovascular risk in diabetes) and ADVANCE (action in diabetes and vascular disease: Preterax and Diamicron MR controlled evaluation) studies[4,5] — the former pursuing an intensive treatment arm of HbA_{1c} less than 6% and the latter HbA_{1c} of less than 6.5%.

Both studies failed to demonstrate an improvement in cardiovascular outcomes over 3.5–5 years. In fact, in the ACCORD study there was a higher mortality rate in the intensive treatment arm, which led to the 'glycaemic control' part of the study being terminated early.[4]

According to data from the United Kingdom prospective diabetes study (UKPDS) 53% of patients initially assigned to treatment with a sulphonylurea required long-term insulin therapy within six years of follow-up.[6] So it is not uncommon for patients with T2DM to progress to a stage where insulin is required for better control.

Mr DD is experiencing symptoms of hyperglycaemia (tiredness, a lack of energy and nocturia) and his HbA_{1c} is 8.6%, which falls outside the agreed target. He has previously had an adverse reaction to pioglitazone and so his GP believes that it is time to consider insulin therapy.

Question 2: Which insulin regimen is the most appropriate?

Traditionally in T2DM oral agents were stopped when insulin was started. However, current practice now recognises that there are often advantages to combining insulin with oral agents. Potential benefits of this approach include less weight gain, reduced risk of hypoglycaemia, better glycaemic control while the insulin dose is being titrated and smaller doses of insulin are needed.[7] Current opinion does not favour any particular insulin regimen. However, a 3-year clinical study 'treating to target in type 2 diabetes (4-T)' is underway. It aims to compare the safety and efficacy of adding analogue biphasic, prandial, or basal insulin to metformin and sulphonlyurea in T2DM. A preliminary 1-year analysis of the results indicates that biphasic and prandial insulin may give better glycaemic control but appear to cause more weight gain and hypoglycaemia than basal insulin.[8]

The various different insulin regimens should be discussed with the patient so that a joint decision is made as to which regimen to start. If at any stage the original choice is considered inappropriate another regimen may be tried. Four of the most common insulin regimens are discussed below.

1. Once daily intermediate-acting or long-acting insulin

This insulin regimen is commonly given either at bedtime or during the day. Once-daily insulin is beneficial in that it involves the minimum number of daily injections yet usually improves glucose control significantly, especially when introduced in addition to patients' usual oral glucose-lowering medicines. It can also be started in a community setting and dose titration may be undertaken effectively and safely by patients who have received appropriate education.[9] Bedtime intermediate-acting doses may be particularly helpful if the patient is known to experience night-time or early-morning hyperglycaemia. Long-acting insulin (offering 24-hour, 'peakless' control) may be given at any time of the day, as long as it is at roughly the same time each day.

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This type of regimen is particularly beneficial for those who may experience hypoglycaemia with an intermediate-acting product or for those who require someone else to inject the insulin (such as a district nurse) because it only requires one injection and can be given during the day-time. Suitable examples of insulin to use in a once-daily regimen include Insulatard® or Humulin I® (as intermediate-acting insulin) and glargine (Lantus®) or detemir (Levemir®) as long-acting, analogue insulin. NICE recommend that when starting a once-daily insulin regimen metformin and sulphonylureas are continued, but that the continuation of sulphonylurea is reviewed if hypoglycaemia occurs.[3]

2. Twice-daily pre-mixed insulin

This regimen is popular because it tends to offer better post-prandial control than once-daily options. It is also easy to explain to patients and only involves two injections per day — one in the morning before breakfast and the second in the evening before the evening meal. The disadvantages include a higher risk of hypoglycaemia (especially mid-morning and at night) and a potential for more weight gain, because most patients tend to need a mid-morning and bedtime snack. There is also less flexibility with pre-mixed insulins because they contain fixed ratios of short and long-acting insulin and each injection given determines approximately the next 12 hours of required carbohydrate intake.

Suitable pre-mixed insulins include

There are many variables to consider when starting insulin and the prescriber needs to be aware of a number of factors including the degree of insulin resistance, level of hyperglycaemia, whether or not oral therapies are to continue, co-morbidities, ease of future contact with the patient and whether they have help at home should hypoglycaemia occur before deciding on a suitable dose.

either conventional short-acting plus isophane insulin, such as Mixtard 30® or Humulin M3® or analogue mixed insulin, such as NovoMix 30®, Humalog Mix 25®or Humalog Mix 50®. The analogues are preferable in situations where hypoglycaemia is troublesome or if injecting 20–30 minutes before food is a problem (because analogues may be injected immediately before food). NICE recommend that when starting a twice-daily insulin regimen metformin is continued — the sulphonylurea should be continued to begin with, but stopped if hypoglycaemia occurs.[3]

3. Prandial insulin (three times daily)

In this regimen insulin is injected three times daily, before each main meal. It offers more flexibility in the timing and content of meals than those already discussed and generally gives better glycaemic control. Although one of the obvious disadvantages is that it involves more daily injections. These days the rapid-acting analogue insulins (aspart [Novorapid®], lispro [Humalog®] or glulisine [Adipra®]) are used in preference to soluble insulins because they give better postprandial glucose control and have a lower potential for causing hypoglycaemia. They may be injected up to 15 minutes before food.

4. Basal bolus insulin (prandial insulin plus long-acting insulin)

As for the previous regimen, basal bolus therapy offers good flexibility in the timing and content of meals. It involves three daily injections with meals and one or two injections of 'basal' or 'background' insulin — requiring 4–5 daily injections. This regimen would not usually be chosen at the start of insulin therapy for a person with T2DM but if other regimens have failed to achieve optimal glycaemic targets, the patient may be switched to this one. It is considered the regimen that most closely mimics normal physiological insulin release. It requires frequent blood glucose testing by the patient. However, for those who are adequately educated on dose adjustment, it may offer greater independence with lifestyle and dietary freedom.

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Question 3: What is a suitable starting dose of insulin?

The initiation of insulin therapy may be considered more an 'art' than a 'science' — there is no substitute for experience when beginning and titrating insulin safely. There are many variables to consider when starting insulin and the prescriber needs to be aware of a number of factors including the degree of insulin resistance, level of hyperglycaemia, whether or not oral therapies are to continue, co-morbidities, ease of future contact with the patient and whether they have help at home if hypoglycaemia should occur, before deciding on a suitable dose. The following recommendations are considered general guidelines for starting insulin and for dose titration.

- ☐ Once daily intermediate- or long-acting insulin plus oral agents.
  Start with 10–20 units (or 0.2 units per kg body weight). Titrate the dose so that a pre-breakfast glucose reading of 5.5–6 mmol/L is achieved with no nocturnal hypoglycaemia. It is suggested that the dose is increased by 2 units every three days to achieve this.
- ☐ Twice-daily pre-mixed insulin.
  Begin with 6–10 units bd of pre-mixed insulin. The morning dose needs to be titrated so that it gives a pre-lunch glucose reading of less than 6 mmol/L and the evening dose of insulin needs to be titrated to give a pre-bed glucose reading between 6–8 mmol/L and pre-breakfast reading of 5.5–6 mmol/L. Increases of 2 units daily are recommended to achieve these targets.
- ☐ Prandial insulin (three times daily).
  Begin with a small dose of 2–6 units of insulin before each meal (giving a total daily dose of 10–20 units of insulin) depending on how much carbohydrate is usually consumed at each respective meal. Titrate the dose slowly in increments of 2 units daily to give satisfactory pre-meal and pre-bed glucose readings.
- ☐ Basal bolus insulin (prandial insulin plus long-acting insulin).
  Patients receiving this insulin regimen would not normally continue with oral insulin secretagogue therapy

(sulphonylureas or meglitinides) however, metformin may be maintained. If the patient is already using once- or twice-daily basal insulin continue with this and add in rapid-acting meal-time insulin three times daily, usually at a dose of 6–8 units with each meal. Doses may vary depending on the carbohydrate intake and risk of hypoglycaemia. If the patient is already taking twice-daily pre-mixed insulin add the total daily dose of insulin and subtract 20% (unless considered inappropriate to do so). Give 50% of the total dose as basal insulin and divide the remainder to give as meal-time rapid-acting insulin (bearing in mind the patient's usual eating habits and how much carbohydrate is consumed at each meal). For example, if the patient normally takes NovoMix® 60u in the morning and 40u in the evening, the total daily dose is 100 units. Subtract 20% (20u) which leaves 80u for the basal bolus regimen. Give 40u as basal insulin and divide the remaining 40u between the three main meals of the day (12–14u), depending on how much carbohydrate is usually consumed at each meal. Adjust the basal insulin every 3–4 days to achieve a pre-breakfast glucose level of 5.5–6 mmol/L. Adjust the prandial insulin to achieve satisfactory glucose levels before the next meal or 2 hours after the meal.[10]

The introduction of insulin should run in parallel with patient education. To empower patients and provide enough confidence for them to self-manage their diabetes they need to know the importance of using regular insulin (i.e. not missing doses), glucose level monitoring, insulin dose titration and the recognition, treatment and avoidance of hypoglycaemia.

Question 4: What barriers do patients often have to starting insulin?

It is normal and understandable that many patients have barriers to starting insulin. However, for a large number, once they have actually started insulin, their concerns and fears are reduced and many comment that insulin therapy is not as bad as they thought it would be. Examples of some of the most common barriers are: fear of injecting, concerns about hypoglycaemia and weight gain, coping with illness when receiving insulin, ability to drive and cultural concerns in some patient groups.

Mr DD is a delivery driver and his main fears are that he may not be able to continue his job if he were to start insulin therapy.

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Question 5: What are the Driver and Vehicle Licensing Agency requirements for those with diabetes?

By law it is required that people who drive and use insulin must inform the driver and vehicle licensing agency — or DVLA. (Those who are treated with tablets also legally have to inform the DVLA if they have another 'relevant condition or complication'. For those taking tablets who have no other 'relevant condition or complication' it is advisable to inform the DVLA). The DVLA will respond by sending the patient a 'diabetic 1' form, which asks for more information and the name and address of GP and/or hospital doctor.[11]

If the patient drives a 'large goods vehicle' or 'passenger carrying vehicle' the introduction of insulin means that they must stop driving these vehicles immediately and their licence to do so will be removed.[11]

Because Mr DD holds a standard driving licence he will need to inform the DVLA if he starts to use insulin. However, as long as there are no complications that will compromise his ability to drive safely (which need to be verified by his doctor) he should be able to continue to drive. He would need to be educated about the risk of hypoglycaemia and how to avoid and treat it, should it occur. ✣

Declaration of competing interests

The authors declare that they have no competing interests.

Elizabeth Hackett, principal pharmacist for diabetes, **Winston Crasto,** diabetes research registrar, University Hospitals Leicester

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