Type 2 diabetes: The options for managing glycaemia in primary care

Roger Gadsby

Article points

1. The UK Prospective Diabetes Study provided convincing proof of the value of good glycaemic control in type 2 diabetes.
2. If nutrition and exercise alone are not successful in giving good glycaemic control, oral agents need to be added.
3. The idea of adding once-daily long-acting insulin and continuing oral agent therapy for people with type 2 diabetes is quite a straightforward concept, which can easily be carried out in the community.
4. A recent study by Davies et al (2005) gives great reassurance that people with type 2 diabetes can, using self-monitoring of blood glucose and a simple titration algorithm, titrate their insulin treatment dose to control their glycaemia very successfully.

Key words

- Type 2 diabetes
- Glycaemia
- Insulin
- Dose titration

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The UK Prospective Diabetes Study (UKPDS; UKPDS Group 1998a) provided convincing proof of the value of good glycaemic control in type 2 diabetes. This article summarises the options for managing glycaemia in the primary care setting – from nutritional and exercise approaches to the use of oral agents and insulin therapy.

There is high quality evidence from randomised controlled trials in both type 1 and type 2 diabetes to show that intensive control of blood glucose (giving HbA_{1c} measurements of 7% or less) reduces the risk of adverse outcomes. The evidence in type 1 diabetes comes from the Diabetes Control and Complications Trial (DCCT; DCCT Research Group, 1993), in which an intensively controlled group with an average HbA_{1c} of 7% had a 47% reduced risk of severe retinopathy, a 54% reduced risk of developing microalbuminuria and a 60% reduced risk of neuropathy compared with a standard treatment group who had an HbA_{1c} of 9%.

In type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) provided convincing proof of the value of good glycaemic control (UKPDS Group, 1998a). In the study, 5102 people with newly diagnosed type 2 diabetes were initially managed with 3 months' diet treatment. Then 4209 of these who were asymptomatic and had fasting plasma glucose levels between 6 and 15 mmol/l were randomised into an intensively treated group, who had an average HbA_{1c} of 7.9%, and a conventionally treated group, who had an average HbA_{1c} of 7%. Follow up was for 12 years on average. The intensive group had 12% less risk of any diabetes-related adverse endpoints, 25% fewer adverse microvascular endpoints and 16% fewer myocardial infarctions (this figure for major macrovascular outcomes did not reach statistical significance). Neither sulphonylurea nor insulin therapy showed any advantage over the other, but a group of obese patients randomised to metformin had substantially better macrovascular outcomes (UKPDS Group, 1998b).

This UKPDS glycaemic data has also been published in an epidemiological form in which it can be shown that adverse outcomes are reduced given any reduction in HbA_{1c} level even if a target of 7% is not reached, and thus a reduction of HbA_{1c} from 10% to 9% is of benefit (Stratton et al, 2000).

The diabetes section of the Quality and Outcomes Framework of the new General Medical Services (nGMS) contract for general practitioners recognises the importance of glycaemic control in diabetes by giving 30 points for glycaemic control: 3 for HbA_{1c} process measurements and 27 for reaching HbA_{1c} quality targets (British Medical Association, 2003).

Achieving good glycaemic control: The role of nutrition and exercise

The emphasis today in diabetes is away from the concept of diet, towards the concept of healthy eating. This concept of healthy eating is important for all people and its adoption by all members of the family will help in management.

A simple written guide can be used to reinforce healthy eating messages. A full assessment can be given by a dietitian for those who need more detailed advice.

Weight reduction in those who are overweight is a vital part of type 2 diabetes management. There is clear evidence that weight reduction and exercise can prevent the onset of diabetes in people who are especially at risk (i.e. those with impaired glucose tolerance; Tuomilehto et al, 2001). Regular weighing and encouragement of weight loss (in those who are overweight) at each practice diabetes visit can help in this difficult area. Some people also benefit from attendance at peer-support groups such as 'Weight Watchers' and similar groups.

Encouraging exercise in diabetes is another vital part of good glycaemic control, and has been shown to help prevent the onset of diabetes in susceptible individuals (Tuomilehto et al, 2001).

It is important that advice about exercise should be realistic, simple, individualised, and enjoyable. Gentle walking for 20 minutes a day is a realistic goal in self-management for many people with diabetes. In parts of the UK 'walking for exercise' schemes have been established where people are invited to join in set walks which are organised and led by local volunteers.

It is usual to give most overweight people newly diagnosed with type 2 diabetes initial nutrition and exercise advice and to review them at 3 months to see if it has been successful at reducing HbA_{1c} levels to target.

If nutrition and exercise alone are not successful in giving good glycaemic control, oral agents need to be added.

Initial oral agent monotherapy

NICE guidance on initial monotherapy choice

For those overweight: Metformin as initial monotherapy

The National Institute for Health and Clinical Excellence (NICE; formerly the National Institute of Clincal Excellence) guideline on glycaemic control in type 2 diabetes (NICE, 2002) recommends that metformin be the initial monotherapy of choice in all people who are overweight (defined as a body mass index [BMI] greater than 25 kg/m^2).

This is because of the evidence that metformin has the added value of reducing cardiovascular events (UKPDS Group, 1998b) in addition to its effect on blood glucose lowering. In overweight patients who are intolerant of metformin, a glitazone can be used as initial monotherapy.

For those with BMI below 25 kg/m^2: Sulphonylurea as initial monotherapy

The NICE guideline (NICE, 2002) says that metformin ought to be considered as initial monotherapy in those who are normal weight or overweight. However, there are a small number of patients newly presenting with type 2 diabetes who are thin; who are eating a healthy, low sugar diet; who are exercising well; and who have significant hyperglycaemic symptoms of thirst and polyuria. In this group, beta-cell dysfunction probably plays the most important part in the aetiology of their diabetes.

A choice of sulphonylurea as the initial monotherapy is recommended by NICE in this situation (NICE, 2002).

A close watch needs to be kept on such people by seeing them every few weeks, monitoring the effects of the sulphonylurea by measuring fasting glucose levels, and titrating the dose up accordingly.

Combining oral therapies

If the maximum tolerated dose of one oral hypoglycaemic agent in monotherpy does not control glycaemia adequately, a second agent needs to be added. The options are outlined below.

Metformin plus sulphonylurea

The addition of a sulphonylurea to metformin is recommended by the NICE guidelines (NICE, 2002). This combination, with its complementary modes of action, proven efficacy, and cost-effectiveness, has been widely used over the past 20-plus years.

One disadvantage of the combination is the need to take tablets twice a day. Using generic

Page points

1. The emphasis today in diabetes is away from the concept of diet, towards the concept of healthy eating.
2. Weight reduction in those who are overweight is a vital part of type 2 diabetes management.
3. If nutrition and exercise alone are not successful in giving good glycaemic control, oral agents need to be added.
4. The National Institute for Health and Clinical Excellence (NICE) guideline on glycaemic control in type 2 diabetes (NICE, 2002) recommends that metformin be the initial monotherapy of choice in all people who are overweight.
5. It also says that metformin ought to be considered as initial monotherapy in those who are normal weight or underweight.

metformin and generic gliclazide at respective doses of 1000 mg and 160 mg twice a day means a total tablet load of four tablets taken twice a day.

Metformin plus glitazone

The advantage of this combination is that it has a very low risk of causing hypoglycaemia and uses two therapies that target insulin resistance, so it may be helpful in obese individuals.

If the combination product of rosiglitazone plus metformin in one tablet is used it may be able to reduce the number of tablets required to one of the combination tablets taken twice a day. One disadvantage is that because of the slow onset of action of the glitazone, it may take several months before reductions in HbA_{1c} measurements are seen.

Sulphonylurea plus glitazone

This combination can be used if the patient is intolerant of metformin.

The next step

If therapy with two agents at maximum tolerated doses does not reduce HbA_{1c} to target there are several possible options.

- ***Add acarbose.*** In practice, because acarbose produces so many gastrointestinal side effects, and reduces the HbA_{1c} by less than 1% (Chiasson et al, 1994), this is hardly ever considered.
- ***Add a third oral agent and so use a triple therapy.*** Triple therapy with metformin/sulphonylurea/glitazone is becoming quite widely used. Rosiglitazone now has a license to be used in triple therapy. It may defer the need for insulin for a time, and is especially helpful where people have a great reluctance to go on insulin through fear of injections or because of employment concerns.
- ***Add insulin.*** Alternatively, the patient can be initiated on to insulin therapy, as described below.

Using insulin with oral agents in type 2 diabetes

There is no strong evidence base to determine exactly when insulin therapy should be introduced, but it should be considered in patients who meet the following criteria (Gadsby, 2003).

- Poor glycaemic control as evidenced by persistently elevated HbA_{1c}. There is no consensus as to exactly what elevated level of HbA_{1c}, but at least above the 7.4% target.
- Symptoms of polyuria, polydipsia, nocturia and/or recurrent infections such as balanitis and thrush.
- Currently receiving maximium tolerated dosage of oral agents.
- Already have optimised lifestyle changes.

A key factor that will need to be addressed is the individual's views, attitudes and fears. These usually involve worries about the fear and pain of injections, and the risks of hypoglycaemia. The needles used for insulin injections today are very short and thin, and as a result injections are almost pain-free. The risks of hypoglycaemia may be minimised by using simple insulin regimen, and continuing oral agent therapy with metformin (Gadsby, 2003).

Initiating once-daily, long-acting insulin therapy in type 2 diabetes in primary care

Insulin initiation was traditionally carried out in secondary care, usually by diabetes specialist nurses. In some parts of the UK diabetes specialist nurses are so busy that waiting lists of people with type 2 diabetes needing to go on insulin have developed. The idea of adding once-daily long-acting insulin and continuing oral agent therapy for people with type 2 diabetes is quite a straightforward concept that can easily be carried out in the community. A number of practice nurses are now learning how to do this with support and supervision from experienced diabetes nurses through education programmes (e.g. Warwick Diabetes Care, 2005).

When intiating a person with type 2 diabetes on to insulin therapy, the steps outlined in *Table 1* should be followed (Gadsby, 2003).

Once-daily long-acting insulin or twice-daily premixed insulin for insulin initiation?

The traditional regimen for starting someone with type 2 diabetes on insulin therapy used to be to use a twice-daily mixed insulin such as biphasic isophane insulin and stop all oral hypoglycaemic medications. It is now clear from a number of studies that continuing oral medications when beginning insulin therapy is helpful in reducing weight gain and minimising the total units of

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1. A choice of sulphonylurea as the initial monotherapy is recommended by NICE in people who are thin; who are eating a healthy, low sugar diet; who are exercising well; and who have significant hyperglycaemic symptoms of thirst and polyuria.
2. If the maximum tolerated dose of one oral hypoglycaemic agent in monotherpy does not control glycaemia adequately, a second agent needs to be added.
3. Options include: the addition of a sulphonylurea to metformin; metformin plus a glitazone; or a sulphonylurea plus a glitazone.
4. There is no strong evidence base to determine exactly when insulin therapy should be introduced, but it should be considered in patients who meet a range of criteria (including persistently elevated HbA_{1c}, or symptoms of polyuria, polydipsia or nocturia).

insulin needed to give good glycaemic control (Douek et al, 2005).

A recently published paper compared the use of the once-daily long-acting insulin glargine and continued use of oral agents with the use of twice-daily biphasic isophane insulin (Janka et al, 2005). It found that the mean HbA_{1c} decrease from baseline was more pronounced and more patients reached an HbA_{1c} target of 7% or less without nocturnal hypoglycaemia in the insulin glargine group than in the twice-daily premixed insulin group.

What to do if once-daily insulin plus tablets becomes ineffective at controlling glycaemia

There has been discussion among health professionals that once-daily insulin plus tablets may not be enough to control glycaemia over time. There is as yet little or no trial evidence to tell us how long the simple regimen of once-daily insulin will suffice or whether there will be groups of patients in which it will fail to control glycaemia adequately. There is also no definitive evidence as to what to do next, so a number of suggestions have been made by healthcare professionals.

One suggestion could be to change to a twice-daily premixed insulin regimen. Another approach would be to add an injection of a short-acting analogue insulin with the main meal of the day. The dose of short-acting insulin can then be titrated up using self-monitored blood glucose readings. Once this two-dose insulin regimen is no longer sufficient to control glycaemia, a second injection of short-acting insulin could be given with the next biggest meal of the day. Again, if this was not sufficient a third short-acting injection could be given with the other meal of the day. This would then be the full basal–bolus regimen of one injection of short-acting insulin with each meal with one injection of long-acting insulin at night, which is commonly used in type 1 diabetes.

Insulin dose titration by patients or doctors?

A recent paper (Davies et al, 2005) compared two dose-titration regimens for once-daily insulin glargine in a large cohort of nearly 5000 people with poorly controlled type 2 diabetes. In one arm of the trial, the dose titration was made on a weekly basis by the doctor. In the other arm, the dose titration of a 2-unit increase was made by the person with diabetes every 3 days after self-monitoring of blood glucose. The paper concluded that insulin glargine has a good safety profile and is effective in improving glycaemic control in a large diverse population with long-standing type 2 diabetes. The patient-administered titration algorithm conferred significantly improved glycaemic control with a low incidence of severe hypoglycaemia compared with the physician-managed titration.

This paper gives great reassurance that people with type 2 diabetes can, using self-monitoring of blood glucose and a simple treatment algorithm, titrate their insulin treatment dose to control their glycaemia very successfully.

This evidence supports the ideas for patient empowerment outlined in Standard 3 of the diabetes National Service Framework (Department of Health, 2001). ■

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Table 1. Steps that should be followed when initiating a person with type 2 diabetes on to insulin therapy (Gadsby, 2003).

Before start of insulin

- Teach self-monitoring of blood glucose monitoring if patient is not already practising it
- Revise and reinforce dietary principles

Initiation of insulin

- Continue treatment with metformin and the sulphonylurea
- Teach insulin injection technique
- Define initial dose of insulin (glargine or other long-acting insulin) – one injection in the evening
- Safe starting dose = fasting glucose level as units of insulin, i.e. if fasting glucose is 10 mmol/l, starting insulin dose is 10 units
- Give verbal and written instructions about increasing glucose dose by 2 units if three consecutive fasting blood glucose measurements are above 5.5 mmol/l
- Teach about hypoglycaemia symptoms and treatment, sick day rules and driving regulations
- Give contact telephone number for advice and help

Follow up

- By phone after a couple of days and then individualise frequency of calls depending on progress, on need to alter insulin dose and on blood glucose control
- Measure HbA_{1c} every 3 months until stabilised

Page points

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2. Another approach would be to add an injection of a short-acting analogue insulin with the main meal of the day.
3. The dose of short-acting insulin can then be titrated up using self-monitored blood glucose readings.
4. A recent paper (Davies et al, 2005) concluded that insulin glargine is safe and effective in improving glycaemic control in a large diverse population with long-standing type 2 diabetes.
5. A patient-administered titration algorithm conferred significantly improved glycaemic control with a low incidence of severe hypoglycaemia compared with a physician-managed titration.
6. This evidence supports the ideas for patient empowerment outlined in Standard 3 of the diabetes National Service Framework.

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