



# Progression of type 2 diabetes – Do we provide the best treatment at the most appropriate time?

A report from the London leg of a series of roadshows sponsored by Abbott Diabetes Care. The event was held on 11 February 2008.

Abbott Inspire is a new loyalty programme recently launched in the UK and aimed at healthcare professionals. Abbott Inspire includes a variety of benefits such as learning options, technology and general diabetes support, and regular communication through a variety of newsletters, for example. Diabetes Dilemmas was a series of local roadshows that focused on the progression of type 2 diabetes and whether healthcare professionals provide the best treatment at the most appropriate time. This is a report from the London leg of the roadshow that took place on 11 February 2008. The series of roadshows focused on lifestyle and weight management, stepwise treatment algorithms, new therapies, and

blood glucose monitoring and how it fits into the management of type 2 diabetes.

#### Speakers at the London Roadshow:

- Mike Baxter (Consultant Diabetologist, Ashford & St Peters)
- Gwen Hall (Diabetes Specialist Nurse, Haslemere; and Associate Editor, *Diabetes & Primary Care*)
- David Haslam (Clinical Director, National Obesity Forum; and GP, Hertfordshire).
- Debbie Hicks (Nurse Consultant – Diabetes; and Editor, *Journal of Diabetes Nursing*)

The International Diabetes Federation (IDF) estimates that, globally, approximately 190 million people have diabetes; they further predict that this number will rise to over 360 million by the year 2025 (IDF, 2006). In the UK, over 2 million people have diabetes (approximately 3% of the population; Diabetes UK, 2006). The majority of the UK population with diabetes have type 2. Diabetes UK have calculated that the number of diabetes related deaths will increase by 25% in the next 10 years (Diabetes UK, 2006). Therefore, the NHS has a huge financial burden – with (due to under-reporting of diabetes upon hospital admission a conservatively estimated) 9% of its annual budget spent on treating diabetes and its complications. (This amounts to, approximately, £5 billion a year, £13.7 million per day, £570 000 per hour, £9500 per minute and £158 per second.) The prescribing budget accounts for approximately 8% of the total, with spend on diabetes related complications accounting for the vast majority of costs. The above costs are predicted to rise by 10% by

the year 2011 due to the increasing number of people with diabetes.

#### Can we prevent diabetes?

By investing in preventing type 2 diabetes, its human and economic costs can be significantly reduced. There are a number of modifiable risk factors that, if targeted, can lower the risk of developing type 2 diabetes (such as weight and activity levels).

Findings of the US-based Diabetes Prevention Program (DPP) demonstrated a 58% reduction in progression to type 2 diabetes in its intensive nutrition and lifestyle modification arm (DPP Research Group, 2002). Those in the metformin arm had a 31% reduction in progression to type 2 diabetes. The study randomised 3234 people with impaired glucose tolerance to intensive lifestyle, 850mg metformin OD or placebo; with average follow up of 2.8 years.

Although metformin reduced risk of developing type 2 diabetes, lifestyle modification delays the progression to diabetes significantly more. The study authors concluded that approximately 150 minutes of

moderate physical activity a week, combined with weight loss can delay progression to diabetes.

#### Intensive diabetes management: Benefits

The UK Prospective Diabetes Study (UKPDS; 1998a and b) focused on glycaemic and blood pressure control and the financial implications of type 2 diabetes. The data demonstrated that controlled glycaemia and blood pressure can significantly lower the risk of macro- and microvascular complications associated with diabetes. They also demonstrated that for every 1% reduction in HbA<sub>1c</sub> there is a:

- 21% reduction in risk of all diabetes-related end points
- 21% reduction in diabetes related deaths
- 14% reduction in myocardial infarction
- 37% reduction in microvascular complications.

Evidence, 'and common sense' [Debbie Hicks], have shown that in people newly diagnosed with diabetes, the increased therapy costs of intensive glycaemic and blood pressure control are largely offset by significantly reduced costs of complications.



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## Metformin and sulphonylureas: Tried and tested?

### Metformin

Metformin is derived from the plant *Galega officinalis*. The plant has been used since the middle ages to treat the symptoms of diabetes. Metformin was first described in the late 1950s, and has been used as an oral antidiabetic agent in the UK for the last 50 years.

Current UK clinical guidance recommends that metformin be used as the first-line antihyperglycaemic for the majority of people with type 2 diabetes. There are two main mechanisms by which metformin lowers blood glucose levels:

- it enhances sensitivity of tissues to insulin
- it decreases hepatic glucose output.

Owing to its mechanisms of action, hypoglycaemia is highly unlikely.

Metformin is also weight neutral and it lowers fibrinogen levels, thus reducing the number of thrombotic events. Other key benefits include its inexpensiveness and its long time use leading to clinician confidence in its effectiveness.

### Sulphonylurea

Similar to metformin, sulphonylureas (SUs) have been used in clinical practice for approximately the last 50 years, thus also leading to clinician confidence. SUs stimulate pro-insulin release by pancreatic beta-cells. They have been shown to lower HbA<sub>1c</sub> by approximately 1.5–2% (reviewed in [DeFronzo, 1999](#); although in practice, Gwen Hall said that this probably averages out to 1%). However, they are associated with weight gain (they should therefore be avoided in overweight and, particularly, obese people) and, because they do not act in a glucose-dependent manner, hypoglycaemia. SUs are also inexpensive.

### Concordance versus compliance

**Concordant:** *'In agreement; consistent'*.

**Compliant:** *'Disposes to agree with others or obey rules, especially to an excessive degree; acquiescent.'*

*Meeting or in accordance with rules or standards'.*

These are the Oxford English Dictionary's definitions of 'concordant' and 'compliant'. 'To effectively modify patient management and to solve problems relating to "compliance", we should seek *concordance* with the patient,' said Debbie Hicks. Concordance can be difficult for the patient as he or she may be on >20 tablets a day. However, there are a number of strategies available.

- Empower patients to understand their medications.
- Switching to once-daily agents.
- Switching to combination therapies.
- Using dossett box systems.

After lifestyle modification, metformin is still the first-line treatment of choice for people with type 2 diabetes, followed by SUs and thiazolidinediones. The most difficult challenge for healthcare professionals is to ensure that their patients are taking their medications as prescribed. What are the therapeutic options once diabetes control begins to deteriorate on metformin and SUs?

### New antidiabetic therapies

In 1967 [Perley and Kipnis](#) demonstrated that orally administered glucose has a higher effect on insulin secretion than an equivalent of intravenously administered glucose. The difference between the two was termed the 'incretin effect' by [Nauck et al in 1986](#), and the hormones stimulating insulin secretion the 'incretins'.

The two main incretin hormones are GLP-1 and GIP (glucagon-like peptide 1 and glucose-dependent insulinotropic peptide, respectively; GIP is also known as gastric inhibitory peptide). GLP-1 is made and secreted by the L cells of the ileum and colon, it acts upon the pancreatic alpha- and beta-cells, the gastrointestinal tract, the central nervous system, the lungs and the heart. GIP is synthesised and secreted by the K cells of the jejunum and duodenum and

it acts primarily on pancreatic beta-cells and adipocytes.

### Incretin mimetics

#### Glucoregulatory roles of GLP-1

GLP-1 is secreted within minutes of food intake. Its glucoregulatory functions include the following.

- It enhances glucose-dependent insulin secretion from pancreatic beta-cells.
- It slows gastric emptying.
- It promotes satiety, thus reducing appetite.
- It lowers postprandial glucagon secretion from pancreatic alpha-cells, thus lowering hepatic glucose output.

#### GLP-1 as a therapeutic target

In response to meals, GLP-1 and GIP potentiate *glucose-dependent* insulin secretion. In people with type 2 diabetes the incretin effect is markedly reduced. This reduced effect can be attributed to significantly lower postprandial GLP-1 levels in people with type 2 diabetes than in those with normal glucose tolerance.

GIP levels appear to be normal in people with type 2 diabetes – however, it appears to have lost some of its insulinotropic effect. Though impaired, GLP-1 secretion in people with type 2 diabetes is able to elicit an insulin response. Therefore, GLP-1 offers a viable therapeutic option within the incretin system. Exenatide is a GLP-1 mimetic, and the first in class.

However, GLP-1 has a very short half-life and is rapidly inactivated after secretion: within 2 minutes. As a treatment option, GLP-1 must therefore be administered continuously by infusion in order to have any effect on blood glucose levels, thus making this an inconvenient option for treating type 2 diabetes. GLP-1's inactivating enzyme could, on the other hand, be a suitable target (dipeptidyl peptidase-4; DPP-4). DPP-4 inhibitors are in various stages of development, sitagliptin (the first in class) is discussed later.

Yet another treatment option in the incretin



system for an antidiabetic agent is for a mimetic such as exenatide. Exenatide is a synthetic form of exendin-4 and shares 53% homology with endogenous human GLP-1 and is found in the saliva of the Gila monster, a venomous lizard from North America. Exenatide is resistant to DPP-4-mediated inactivation and has a half-life of 144 minutes.

There is a wealth of evidence for exenatide in improving glycaemia in people with type 2 diabetes. These include extensive phase III trials with open label extensions in patients receiving metformin, sulphonylurea or a combination of both; there are also comparator trials with insulins ([ALL REFS X3](#)).

#### Case studies

Mike Baxter presented a number of case studies demonstrating the effectiveness of exenatide as an antidiabetic agent: all of his cases demonstrated clinically significant weight loss; some cases were able to stop their insulin injections as a result of the treatment.

#### DPP-4 inhibitors

Sitagliptin is the first in class of DPP-4 inhibitors licensed for use in the UK as an antidiabetic agent. Recently its license has been extended to include its use in dual and triple therapy with metformin alone or with metformin and an SU. There is evidence demonstrating sitagliptin's safety and efficacy in people with type 2 diabetes as add-on therapy to metformin versus metformin alone; as add-on therapy with pioglitazone versus pioglitazone alone; and as add-on to ongoing metformin therapy versus add-on glipizide to ongoing metformin therapy ([REFS](#)).

#### The endocannabinoid system

Endocannabinoids are synthesised on demand from lipid precursors in the post-synaptic cell of the central nervous system. They go on to activate CB1 receptors, which play a key role in food intake, energy balance, and lipid and

glucose metabolism. Rimonabant, the first in class that acts on this pathway, has been shown to lower weight in obese people with or without type 2 diabetes. It also lowers HbA<sub>1c</sub> levels by an average of one percentage point.

#### The role of insulin

In people without diabetes, a biphasic insulin response begins upon glucose stimulation. The first phase starts with a rapid rise in insulin within a few minutes of blood glucose being raised. The second phase involves the first phase insulin levels returning toward baseline within 6–10 minutes after glucose stimulation, after which it gradually rises again. In people with diabetes, the first phase response after the glycaemic load is either absent or greatly diminished. Data from the UKPDS show that approximately half of those with type 2 diabetes and on an SU from the study population needed insulin therapy. However, it is not that straightforward.

Is it best to leave insulin therapy to the last in the diabetes treatment pathway? The American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) recommend early initiation – as early as second line – especially if glycaemic control is relatively poor or unstable. However, people with type 2 diabetes are likely to progress to a need for insulin on average 7 years after diagnosis.

Insulin has many advantages and disadvantages, these are outlined in *Box 1*.

Insulin therapy should be commenced using a structured education programme that employs active dose titration. Such an approach helps in minimising the disadvantages of insulin use. According to Gwen Hall: 'The choice of insulin regimen should be, primarily, the patient's choice with informed healthcare professional input.'

If Insulin is commenced in a structured and informed manner it can also increase the patient's quality of life ([DOVE Investigators, 2003](#)).

#### Lifestyle and weight management

'Diet and physical activity are effective therapies in treating diabetes,' began David Haslam.

#### The Finnish DPP

Evidence from the Finnish Diabetes Prevention Program ([Knowler et al, 2002](#)) demonstrated that intensive lifestyle management was far superior to placebo and metformin in reducing weight, especially at 6 months; the benefits were clearly apparent at 48 months follow up. The cumulative incidence of diabetes according to the study group was also significantly lower in the lifestyle group compared with the placebo and metformin groups ( $P < 0.001$ ).

Successful weight management in people with type 2 diabetes has been shown to ([REFS](#)):

- Improve diabetes control.
- Improve the lipid profile, particularly increasing high density lipoprotein cholesterol (HDL-c).

#### Box 1. Key advantages and disadvantages of insulin for people with type 2 diabetes.

##### Advantages

- Can be more effective than oral agents, especially if initiated early.
- Regimens are flexible.
- Hypoglycaemic episodes can be limited with appropriate choice of regimen and suitable education.
- Proven improvement in complications, particularly microvascular.

##### Disadvantages

- Disliked by patients.
- A drain on healthcare time owing to time involved to initiate and to the necessary ongoing support.
- If support and education is improper, hypoglycaemic episodes are a risk.
- High doses required if the patient is insulin resistant.
- High cost, although the newer agents are also expensive.

- Improve blood pressure.
- Improve insulin sensitivity.
- Improve self-esteem, thus also improving symptoms of depression and anxiety.
- Improve the patient's day-to-day functional capacity.

### *Exercise recommendations*

#### *Young people*

Young people (5–18 years old) should be encouraged to participate in at least 60 minutes of moderate to vigorous exercise that is appropriate to their age and that includes a variety of activities.

#### *Adults*

Adults (18–65 years old) should be encouraged to participate in 30 minutes of moderate to vigorous exercise 5 days a week; *OR* 20 minutes of vigorous exercise 3 days a week; *OR* an equivalent combination of moderate–vigorous activity *AND* 8–10 muscle strengthening exercises at least 2 days per week.

#### *Older adults*

Older adults (>65 years old) should be advised to follow the same recommendation as for adults as described above but with due consideration for the intensity and type of activity appropriate for specific age *AND* to participate in activities that maintain flexibility and balance.

### *Pharmacological interventions for weight loss*

Drug-based interventions have also been shown to be effective in reducing weight. Orlistat has been shown to produce a greater weight loss than diet alone in obese people without diabetes (Sjostrom et al, 1998) and in obese people with type 2 diabetes (Hollander et al, 1998); and, combined with lifestyle intervention, it has a lower relative risk of progression to type 2 diabetes in obese people (Torgerson et al, 2004). Sibutramine also shows similar benefits in similar groups of patients.

Data from the Rimonabant clinical trials demonstrate its effectiveness in lowering weight over lifestyle intervention alone in obese people with and without type 2 diabetes (REFs).

### *Surgical intervention*

Evidence from the Swedish Obese Subjects (SOS) study clearly demonstrates the benefits of surgical intervention. In the first 6 months after surgery, male patients lost an average of 29.1kg and female patients an average of 26kg. Eighty per cent of the study group were rendered euglycaemic, and 93% of the group with impaired glucose tolerance were rendered euglycaemic.

### *Self-monitoring of blood glucose*

In order to check whether any diabetes medication is having the desired therapeutic effect, self-monitoring of blood glucose (SMBG) is an essential tool that allows both the person with diabetes and the clinician valuable day-to-day information into the action of the prescribed medication. There is an ongoing debate as to the value of SMBG in people with type 2 diabetes. In the last session of the day there was a debate as to the value of blood glucose monitoring. There was a consensus among the audience in London (and also in preceding roadshow events in Oxford, Birmingham, Manchester and Leeds) that SMBG has major benefits for people with diabetes, regardless of type, provided it is linked to a structured education programme and the individual is using the result in a constructive way. Given that there is strong evidence to prove that the major cost from diabetes to the NHS is due to caring for people with complications as a result of their diabetes it seems somewhat strange that we are restricting the very tool that enables people with diabetes to self manage their condition and prevent such costly complications both in terms of financial cost and deterioration in quality of life.

It appears that against current guidance some people are being restricted in the amount

of test strips they can be prescribed: 'A postcode lottery exists,' said Gwen Hall. While some areas are following guidance others are limiting people with type 2 diabetes to, despite there being no evidence to support this practice, one or two pots of strips per year.

The draft NICE guidance, due to be published in May this year (delayed from March/April), currently states that blood glucose monitoring should be available to all newly diagnosed people with diabetes as part of their structured education plan. Debbie Hicks and Gwen Hall stressed the importance of such education to back up monitoring. All those who are capable of understanding results and acting upon them should be allowed to access prescribed test strips, regardless of existing the medication. More frequent monitoring is required for those who are taking medication that could cause hypoglycaemic episodes, such as sulphonylureas and insulin. The frequency and targets to be met should be an informed decision made by the person with diabetes in collaboration with their healthcare team and it should be recorded in their care plan. ■