

HOW WOULD I MANAGE A 68-YEAR-OLD MAN WITH LONGSTANDING TYPE 2 DIABETES WHO HAS SECONDARY FAILURE TO ORAL HYPOGLYCAEMIC AGENTS?

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INTRODUCTION

Type 2 diabetes is a complex condition characterised by a combination of both insulin resistance and reduced pancreatic β cell function, although the contribution of these two major components varies between individuals. Particularly in obese patients, insulin resistance plays a major role in the development of diabetes, although it has often been present for many years before the development of hyperglycaemia. However, with the passage of time, progressive and inexorable loss of pancreatic β cell function is the main factor in determining increasing hyperglycaemia. Although the term 'oral hypoglycaemic failure' is frequently used to describe the situation in which the high blood sugar levels can no longer be controlled on conventional oral agents, it is, in fact, the pancreas rather than the drug therapy which is failing.

CONVENTIONAL TREATMENT OF TYPE 2 DIABETES

In treating Type 2 diabetes it is usual practice to commence with a period of dietary modification alone, unless a formal dietary assessment indicates that limited scope exists for beneficial change in a patient who is either markedly symptomatic or very hyperglycaemic. Although appropriate dietary modification will reduce the levels of hyperglycaemia in most patients, data from the UK Prospective Diabetes Study (UKPDS) indicates that only 18% of patients have adequate glycaemic control after a three month period of dietary therapy.¹ In most patients with Type 2 diabetes, therefore, the introduction of oral hypoglycaemic therapy is required soon after diagnosis.

For the majority of patients who are overweight or obese, metformin is the first choice of oral agent, and the UKPDS has clearly demonstrated that in such overweight patients many outcome measures were better on treatment with metformin in comparison to sulphonylureas or insulin.² The mode of action of metformin is complex and not fully understood. However, it enhances peripheral glucose uptake and lowers hepatic glucose output without stimulating insulin production from the pancreas, the overall effect being a net reduction in insulin resistance. Apart from any benefits in long-term outcomes, this results in weight gain on metformin being substantially less than with sulphonylureas or insulin.² Metformin is also effective in non-overweight patients with Type 2 diabetes, although conventionally one of the sulphonylureas has been used as first line oral hypoglycaemic therapy in this group. Sulphonylureas bind to a specific receptor on the pancreatic β cell and act as insulin secretagogues, increasing insulin production by around 25%.³

The UKPDS has demonstrated that, whatever treatment modality is used, a gradual rise in the haemoglobin A_{1c} (HbA_{1c}) concentration recurs over a period of years after an initial response to therapy. In patients treated with sulphonylureas, an approximately linear failure rate (defined by the development of osmotic symptoms or a fasting

plasma glucose >15 mmol/l) occurs with some 7% of patients failing each year. Within six years, 44% of patients had failed on sulphonylurea therapy.⁴ Increasing the dose of the drug can be useful as the HbA_{1c} creeps up, but generally additional benefits from increasing the dose into the higher levels of the sulphonylurea dose range are modest.

When glycaemic control deteriorates on one oral hypoglycaemic agent, it is conventional to try a combination of metformin and a sulphonylurea. These drugs have an additive effect because of their different modes of action and a further, if finite, period of improved glycaemic control can often be achieved.

An additional treatment option, available for several years in the UK, is the α -glucosidase inhibitor, acarbose. This drug is active almost exclusively within the gut and inhibits the hydrolysis of polysaccharides and disaccharides to monosaccharides in the small bowel, slowing down post-prandial glucose absorption, and as a result limiting the post-prandial glucose rise.⁵ Acarbose is effective in improving overall glycaemic control to an extent similar to sulphonylureas and metformin, and can be used in combination with these other drugs. However, although popular in some parts of Europe, the use of acarbose in the UK has been limited by its gastrointestinal side-effects which occur in many patients secondary to partial carbohydrate malabsorption, particularly diarrhoea and excessive production of flatus.

In the case under consideration, I am assuming that conventional combination therapy with a sulphonylurea and metformin, in the maximum tolerated dosage, with or without acarbose, has been instituted and also that, following appropriate dietetic advice, the patient has achieved as much dietary modification and weight loss as is likely to be attainable. In considering future management, I will concentrate on possible strategies for improving glycaemic control, but also briefly consider the importance of treating other risk factors which, in conjunction with hyperglycaemia, may increase the risk of developing both microvascular complications of diabetes and macrovascular disease, particularly hypertension and dyslipidaemia.

IMPROVING GLYCAEMIC CONTROL

It is astonishing that, considering the prevalence of Type 2 diabetes, it is really only since 1998, with the publication of the results of the UKPDS, that we have had clear evidence to support the benefits of strict glycaemic control in reducing morbidity associated with diabetes.⁶ Indeed, the only large randomised trial published previously found no evidence that better glycaemic control improved outcome measures, irrespective of which therapy was used, and even suggested that treatment with a sulphonylurea (tolbutamide) may actually increase cardiovascular mortality.⁷ Prior to 1998, a reasonable strategy for a patient such as the one under consideration might have been to accept suboptimal glycaemic control as long as osmotic symptoms

were absent. While it is certainly the case that good glycaemic control is not possible in all patients, this strategy is no longer acceptable.

IMPORTANCE OF GLYCAEMIC CONTROL – RESULTS OF THE UKPDS

In the UKPDS, patients were randomised to 'conventional' treatment (aiming for a fasting plasma glucose of <15 mmol/l) or 'intensive' treatment (aiming for a fasting plasma glucose <6 mmol/l).⁶ The study also examined whether there were particular benefits from using either insulin or one of two different sulphonylureas (chlorpropamide or glibenclamide) as primary therapy. A total of 1,138 patients were randomised to 'conventional' treatment and 2,729 were included in the main randomisation to the 'intensive' treatment group, with a further 342 overweight patients randomised to receive metformin as primary therapy.² An initial separation in the mean HbA_{1c} occurred very quickly between the two main groups and was maintained throughout the duration of the study. The mean HbA_{1c} over ten years in the 'intensive' treatment group was 7.0%, compared with 7.9% in the 'conventional' treatment group. In association with this, a reduction was observed in the risk of developing any diabetes-related endpoint of 12% ($p = 0.029$) in the 'intensive' treatment group, most of this difference being due to a 25% reduction in the risk of developing microvascular complications ($p = 0.0099$). A statistically significant reduction in overall mortality was not shown, although the trend was favourable. The same was true of the main macrovascular endpoints, but the reduction in myocardial infarction in the 'intensive' treatment group was only marginally short of achieving statistical significance ($p = 0.051$). Further details of the differences between the groups are given in Table 1.

In considering the different treatment modalities, no significant difference was shown between insulin and either of the sulphonylureas in any of the major endpoints. However, in the overweight subgroup (defined as being >120% of ideal body weight), those patients randomised to metformin had much more impressive reductions in any diabetes-related endpoint (32%), diabetes-related death

(42%) and all-cause mortality (36%) compared to the 'conventional' treatment group, all of these reductions being highly statistically significant.² Furthermore, 'intensive' treatment with metformin in this overweight subgroup resulted in a significantly greater effect than 'intensive' treatment with a sulphonylurea or insulin in reducing the risk of developing any diabetes-related endpoint, all-cause mortality and stroke, although glycaemic control was similar with all of the treatment modalities.

THERAPEUTIC OPTIONS TO IMPROVE GLYCAEMIC CONTROL

Returning to the specific patient in question, consideration needs to be given to the use of alternative oral agents or the introduction of insulin. A summary of the various available drugs is given in Table 2.

Alternative oral agents

The last two to three years have seen the introduction of some alternatives to the conventional oral hypoglycaemic agents. Repaglinide, like the sulphonylureas, is a benzoic acid derivative but without the SO₂ component of the sulphonylurea molecule. It appears to bind, at least partly, to a different binding site to the sulphonylureas, the consequence of which is a more rapid onset and shorter duration of action.⁸ Repaglinide, therefore, has the potential to be particularly beneficial in reducing post-prandial hyperglycaemia if administered immediately pre-prandially; it has also been demonstrated to have an additive effect with metformin. However, a disadvantage is the need for multiple daily doses, and overall, in spite of the theoretical advantages, the hypoglycaemic effects appear to be similar to the conventional sulphonylurea, glibenclamide.⁹ On balance, therefore repaglinide would not be of significant therapeutic benefit in this case.

The other major new group of drugs is the thiazolidinediones. The first of these drugs, troglitazone, was briefly introduced in the UK in 1997, but rapidly withdrawn because of fears of hepatotoxicity. During 2000, two new thiazolidinediones, rosiglitazone and pioglitazone, have been licensed for use in the UK, and neither of these newer drugs appears to have any significant adverse effect

TABLE 1
Relative risk of development of diabetes related endpoints in 'intensive' versus 'conventional' treatment of hyperglycaemia in Type 2 diabetes (mean HbA_{1c} 7.0% vs. 7.9%).

| Endpoint | No. of patients with endpoint | | RR in intensive group (CI) | p |
|-------------------------------|-------------------------------|--------------------------|----------------------------|--------|
| | Intensive (n = 2,729) | Conventional (n = 1,138) | | |
| Any diabetes-related endpoint | 963 | 438 | 0.88 (0.79–0.99) | 0.029 |
| Diabetes-related deaths | 285 | 129 | 0.90 (0.73–1.11) | 0.34 |
| All-cause mortality | 489 | 213 | 0.94 (0.80–1.10) | 0.44 |
| Myocardial infarction | 387 | 186 | 0.84 (0.71–1.00) | 0.052 |
| Stroke | 148 | 55 | 1.11 (0.81–1.51) | 0.52 |
| Amputation | 27 | 18 | 0.61 (0.28–1.33) | 0.099 |
| Microvascular disease | 225 | 121 | 0.75 (0.60–0.93) | 0.0099 |
| Renal failure | 16 | 9 | 0.73 (0.25–2.14) | 0.45 |
| Retinal photocoagulation | 207 | 117 | 0.71 (0.53–0.96) | 0.0031 |
| Cataract extraction | 149 | 80 | 0.76 (0.53–1.08) | 0.046 |

on liver function. This group of drugs exert their effect by activating the peroxisome proliferator-activated receptor- γ (PPAR γ), a nuclear receptor expressed mainly in adipose tissue, which increases the transcription of several insulin sensitive genes. This has several metabolic effects, including increased fatty acid uptake, lipogenesis and glucose uptake which result in improved glucose utilisation and insulin sensitivity.¹⁰ However, the thiazolidinediones require an adequate supply of insulin to achieve their maximum glucose-lowering potential; hence their role in secondary oral hypoglycaemic failure may be limited. A more appropriate role may be to reduce exogenous insulin requirements in patients with significant insulin resistance at an earlier stage of the process of progressive pancreatic β cell failure.

Another issue currently limiting the use of both rosiglitazone and pioglitazone is the licensing restrictions on these drugs in the UK. Currently, the use of these drugs is limited to combination therapy with metformin or a sulphonylurea (but not with both, or with insulin). The licence may be extended in the future, but for the moment the thiazolidinediones probably confer few significant benefits over older agents in terms of improving overall glycaemic control.

Insulin therapy

Therefore, it is currently unlikely that additional oral hypoglycaemic agents will adequately improve glycaemic control in this patient, and the next step is the introduction of insulin. The main strategies are:

- the addition of overnight basal insulin to existing oral hypoglycaemic therapy;
- the substitution of sulphonylurea therapy with a more intensive twice daily or multiple injection regimen.

1. Addition of overnight basal insulin.

This is the simplest of the available insulin regimens, the rationale being that an intermediate-acting insulin, most commonly an isophane insulin, administered at bedtime, will reduce hepatic glucose output and fasting hyperglycaemia.¹¹ As these patients do not have absolute insulin deficiency the pancreatic β cell reserve, stimulated by continued sulphonylurea administration, should provide increased mealtime insulin secretion and minimise post-prandial hyperglycaemia. The target fasting plasma glucose on such a regimen should be <6.0 mmol/l.

However, to achieve this quality of glycaemic control many patients, especially the more obese and insulin resistant, will require large doses of insulin, as a result of which further substantial weight gain may occur. In addition, marked post-prandial hyperglycaemia often remains a problem, with the result that the HbA_{1c} does not fall to an unacceptable level.

Although such a regimen may be beneficial initially, personal experience is that it is often necessary within a relatively short period of time to switch to a more intensive insulin regimen, and for many this may be preferable from the outset, i.e. as soon as it is clear that insulin therapy will be needed. Once patients have overcome any initial concerns regarding insulin administration, then two daily injections is little more problematic than one and has the advantage that oral hypoglycaemic therapy can often be discontinued or reduced.

2. Twice daily insulin regimens.

For most patients with secondary oral hypoglycaemic failure, a twice daily insulin regimen will be the most appropriate choice of therapy. An extensive range of pre-mixed insulins is available, these being more convenient than, and just as effective as, free mixing of soluble and isophane insulins using vials and syringes. An added advantage is that the pre-mixed insulins can be administered via a variety of convenient reloadable or disposable 'pen' devices.

Of the different pre-mixed insulin preparations available, a combination of 30% soluble insulin with 70% isophane insulin (e.g. Human Mixtard 30 (Novo Nordisk) or Humulin M3 (Eli Lilly)) suits the majority of individuals, and usually gives reasonable glycaemic control throughout the day. If home blood glucose readings before lunch and/or at bedtime remain elevated, a switch to a combination of 50% soluble insulin and 50% isophane insulin (e.g. Human Mixtard 50 (Novo Nordisk) or Humulin M5 (Eli Lilly)) can be made. Recently, insulin mixtures have become available incorporating a fast-acting insulin analogue (Humalog Mix 25 and Mix 50 (Eli Lilly)). Because the analogue has both a more rapid onset and a shorter duration of action than conventional soluble insulin, these preparations have the advantage that an interval of 30 minutes or more does not need to be left between injecting the insulin and eating a meal to minimise post-prandial hyperglycaemia, and they can be administered immediately before a meal. In addition, there is a reduced risk of late post-prandial hyperglycaemia occurring two to four hours after a meal.

Although individual practises vary, continued sulphonylurea use confers little additional benefit to patients on a twice daily insulin regimen, and my personal practise is to stop sulphonylurea therapy when starting a patient on twice daily pre-mixed insulin. However, with the compelling evidence from the UKPDS demonstrating improved outcomes in obese Type 2 diabetic patients treated with metformin,² a much stronger case can be made for continuing metformin therapy in significantly overweight subjects after starting them on insulin. An additional benefit of this strategy is that metformin may considerably reduce insulin requirements and consequently minimise weight gain.¹² In the future, thiazolidinediones may produce a similar benefit but, to date, licensing restrictions in the UK preclude use of these drugs in this way.

It is important to remember that the risk of hypoglycaemia does increase with the use of insulin twice daily, as well as other, more intensive, insulin regimens. All patients switching to such a regimen should, therefore, be fully educated on the recognition of the symptoms of hypoglycaemia and how to treat these appropriately. They should also have specialist dietetic input to ensure appropriate matching of carbohydrate intake throughout the day to the insulin regimen. With very few exceptions, patients treated with insulin should regularly monitor capillary blood glucose at home, preferably using one of the many meters available to obtain more accurate results and assist in the administration of the optimum dose of the insulin.

3. Intensive insulin regimens.

Intensive insulin regimens using basal overnight insulin supplemented by three to four pre-prandial injections of

soluble insulin, or a fast-acting insulin analogue, are popular with younger patients with Type 1 diabetes to provide more physiological insulin profiles and increased lifestyle flexibility. Continuous subcutaneous insulin infusion (CSII) can fulfil a similar role and may become more popular with improved pump technology. For the majority of older Type 2 diabetic patients with significant residual endogenous insulin secretion, such intensive insulin regimens are unnecessary to achieve adequate glycaemic control and are too complex for most individuals.

GLYCAEMIC TARGETS ON INSULIN THERAPY

There is no glycaemic threshold which, if exceeded, is associated with an increased risk of morbidity and mortality. The ideal, therefore, is to target blood glucose levels to be as near normal as possible. Fasting and pre-prandial capillary blood glucose levels of <6 mmol/l and a target HbA_{1c} of 7%, which was the mean achieved in the 'intensive treatment' group in the UKPDS,⁶ are feasible for many patients but quite unachievable in others, especially some very obese patients with severe insulin resistance. The increased risk of hypoglycaemia with strict glycaemic control also needs to be considered. This may be a particular problem in the elderly and those living alone and, in these groups, more modest glycaemic targets are usually appropriate. The same is true of patients with a serious intercurrent illness in whom life expectancy may be limited.

The setting of target home blood glucose results on an individual basis is, therefore, important depending on specific circumstances. In all patients, however, any reduction in the HbA_{1c} is going to be beneficial in terms of reducing the risk of development or progression of diabetic complications, even when achievement of near-normoglycaemia is not possible. Further data from the UKPDS suggests a 21% reduction in the risk for any diabetes-related endpoint for each 1% decrement in HbA_{1c}, with a 37% reduction in the risk of developing microvascular complications.¹³

TREATMENT OF OTHER CARDIOVASCULAR RISK FACTORS

While glycaemic control is clearly important, it must also be remembered that there may be other major risk factors in a patient with Type 2 diabetes which are likely to contribute to premature morbidity and mortality. These should also be given consideration when measures to improve glycaemic control are being instituted.

Smoking cessation should always be encouraged, although no consistently effective strategy has yet been established. Concurrent hypertension and dyslipidaemia are more readily treated.

HYPERTENSION

Approximately half of all Type 2 diabetic patients will require antihypertensive therapy. The UKPDS showed clear evidence for the benefits of strict blood pressure control in this population; the magnitude of these benefits is almost certainly greater than those obtained with strict glycaemic control in terms of macrovascular disease (34% risk reduction, $p = 0.019$) and microvascular disease (37% risk reduction, $p = 0.0092$).¹⁴ A target blood pressure of 140/80 is recommended,¹⁵ with even lower levels being appropriate in the presence of renal disease.

To achieve this level of control, the majority of patients will require two or more antihypertensive agents and, in the UKPDS, 29% of the 'tight control' group required three or more different drugs.¹⁴ All categories of antihypertensive agents may be considered for use, but β -blockers may confer specific benefits in the presence of pre-existing coronary heart disease, and evidence from the Heart Outcomes Prevention Evaluation (HOPE) study clearly suggests the use of an ACE inhibitor (ramipril) in patients with Type 2 diabetes who have at least one other cardiovascular risk factor, where it will significantly reduce the risk of developing overt cardiovascular disease or nephropathy, the benefits being greater than that attributable to the blood pressure lowering effect alone.¹⁶ ACE inhibitors are also the treatment of choice in most diabetic patients with microalbuminuria or proteinuria.

DYSLIPIDAEMIA

Lipid abnormalities are very common in the Type 2 diabetic population. The large secondary prevention studies investigating the benefits of statin therapy in patients with coronary heart disease have included substantial diabetic subgroups.^{17, 18} These studies have clearly demonstrated the value of a statin in such patients when the serum total cholesterol level is >5 mmol/l.

Even Type 2 diabetic patients without overt coronary heart disease have a very high risk of cardiovascular morbidity and mortality. Target levels for treatment of lipid abnormalities in this group have not been clearly established, but a pragmatic approach is to use risk stratification charts or programs to target those at the most risk. The Joint British Coronary Risk Prediction Chart estimates ten year cardiovascular risk on the basis of age, sex, smoking status, presence or absence of diabetes, systolic blood pressure, plasma total cholesterol and HDL-cholesterol.¹⁹ Certainly, all patients with a ten year risk of cardiovascular disease of >30% should unequivocally be treated, and ideally, if resources allow, the target level for treatment should probably be a ten year risk of >15%. Such patients should be treated as if they already have overt coronary heart disease and receive a statin in an adequate dose to reduce the serum total cholesterol level to <5 mmol/l.

CONCLUSIONS

- Strict glycaemic control in patients with Type 2 diabetes is important in terms of reducing the risk of complications.
- Achievement of good glycaemic control becomes more difficult with time, predominantly due to progressive loss of pancreatic β cell function.
- Many patients will eventually develop secondary failure to oral hypoglycaemic therapy, and adequate glycaemic control can no longer be achieved using dietary modification and conventional oral agents.
- Although several new oral agents have recently been introduced, and may be useful in some situations, the majority of patients with secondary failure to oral hypoglycaemic therapy will require treatment with insulin.
- Several different insulin regimens may be effective but most widely used are:
 - Overnight basal insulin added to existing oral

- hypoglycaemic therapy.
 - Twice daily pre-mixed insulin, with or without continuation of metformin.
- Although near-normoglycaemia is the ideal goal, treatment needs to be individualised. The significant risk of hypoglycaemia with more intensive regimens always needs to be considered, especially in the elderly and those living alone. Home capillary blood glucose monitoring should be introduced, if not already undertaken.

- While glycaemic control is undoubtedly important, all patients with Type 2 diabetes also need to have other cardiovascular risk factors addressed.
- Strict control of blood pressure is particularly important in reducing the risk of both microvascular and macrovascular complications. To achieve this, many patients will require multiple antihypertensive agents.
- Treatment of dyslipidaemia is also important, especially in the presence of pre-existing coronary heart disease or multiple other cardiovascular risk factors.

TABLE 2
Drugs used in the treatment of Type 2 diabetes currently available in the UK.

| Drug | Mode of action | Cause weight gain | Risk of hypoglycaemia |
|---|---|-------------------|-----------------------|
| Biguanides Metformin | Reduce insulin resistance | No | No |
| Sulphonylureas Chlorpropamide Glibenclamide Gliclazide Glimepiride Glipizide Gliquidone Tolbutamide | Insulin secretagogues | Yes | Yes |
| Alpha-glucosidase inhibitors Acarbose | Slow carbohydrate absorption | No | No |
| Sulphonylurea-like agents Repaglinide | Insulin secretagogues | Yes | Yes |
| Thiazolidinediones Pioglitazone Rosiglitazone | Insulin action enhancers | Yes | No |
| Insulin | Reduces hepatic glucose output and increases peripheral glucose utilisation | Yes | Yes |

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