Q J Med 2000; **93**:369–374

Commentary

QJM

Poor glycaemic control in type 2 diabetes: a conspiracy of disease, suboptimal therapy and attitude

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Introduction

Glycaemia in type 2 diabetes is difficult to manage long-term, and despite a wealth of epidemiological evidence, there continued to be doubts, until recently, as to whether intensive glucose control was beneficial. The publication of robust prospective evidence from the United Kingdom Prospective Diabetes Study[1] in September 1998 marked a seminal change.

In type 2 diabetes, there was extensive epidemiological data suggesting that complications were linked to glycaemic exposure,[2] but the UGDP (University Group Diabetes Program)[3] trial had raised doubts about the safety of sulphonylureas in reducing plasma glucose. The DCCT[4] showed in 1993 that tight glycaemic control reduced microvascular complications in type 1 diabetes. The UKPDS provided evidence that tight control was beneficial in type 2 diabetes: patients in an intensively treated group achieved a median HbA1c of 7.0% at 10 years compared to 7.9% in those in a conventionally treated group. This improvement in glycaemic control was associated with a 12% reduction in any diabetes end-points ($p=0.029$) and a 25% reduction in microvascular end-points ($p=0.0099$).[1] However the achieved HbA1c values of the trial were neither the aim of the trial, nor the best glycaemic control that could be achieved, because one of the aims was to address the question of the efficacy and safety of monotherapies. Thus the protocol required, in those randomized to sulphonylurea therapy, that, once the maximum dose was reached, the fasting plasma glucose could rise to 15 mmol/l or to the advent of symptoms before additional pharmacological agents were introduced. The epidemiology analysis of the UKPDS suggested that there was no discernible threshold for the improved outcome with lower glycaemia.

However, in clinical practice optimal glycaemic control is difficult to obtain. Prospective randomized studies have achieved median HbA1c levels of 7.1%[5] and 7.0% in intensively treated patients,[1] but, by definition, 50% of the patients must have had values above this level.

The reasons for poor glycaemic control are complex, and relate to the disease process itself, the inadequacy of therapeutic regimens and the attitudes of both doctors and patients. We discuss here some of the factors related to poor control, and propose some views about the solutions to the problem.

Progressive decline of β-cell function

One finding of the UKPDS was that fasting plasma glucose deteriorated with time. The deterioration in the diet-only policy group strongly suggests that there is progressive deterioration of β-cell function or an increase in insulin resistance over many years. A parallel deterioration was shown in those on sulphonylurea or metformin, suggesting that neither of these agents either accelerated or slowed the rate of decline.

A more detailed analysis of the problem can be undertaken using modelling techniques. β-Cell

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function can be measured by the homeostasis model (HOMA),[6] which showed a reduction from a mean of 50% function at diagnosis to 25% at 5 years.[7] These HOMA estimates of failure rate are concordant with other published estimates.[6,8] There is no current identified therapy that stops the decline in β-cell function and as β-cell function declines, glycaemia increases. 'Sulphonylurea failure' is thus a misnomer: what is observed in the increasing glycaemia of type 2 diabetes over the course of many years as a result of failure of the β cell, not the therapeutic agent. It is also apparent that functional deterioration occurred in those patients in the UKPDS allocated to insulin, and is the explanation why, even when insulin was prescribed in appropriate doses, the HbA1c rose towards that achieved in the DCCT intensive group. This value, about 7%, is probably the best median achievable HbA1c in those who have total β-cell loss.

The rate of failure has been described in detail in the UKPDS patients: failure of sulphonylurea therapy is significantly greater in those who have a higher fasting plasma glucose at diagnosis: in the UKPDS, 61% of those who had fasting glucose >10 mmol/l at randomization required additional therapy at 6 years, compared to 23% of those with a fasting glucose <7.8 mmol/l ($p=0.00001$).[9]

In view of this progressive decline in β-cell function, it is essential to monitor diabetes on a regular basis in order to increase therapy appropriately. In the UKPDS, the fasting plasma glucose rose at a rate of approximately 0.2 mmol/l/year and HbA1c at 0.2% per year (Figure 1). However in the Belfast study,[10] this relatively slow rate of increase occurred only in those patients with the lowest mean fasting plasma glucose at diagnosis (7.5 mmol/l) but half of the patients deteriorated at the significantly faster rate of rate of 1.5 mmol/l/year.

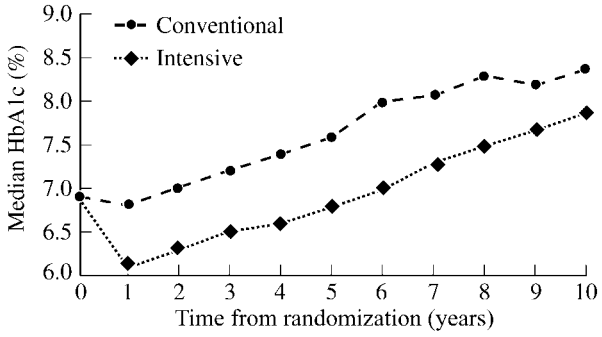

Figure 1. Progressive rise in median HbA1c (*y*-axis) with time in years (*x*-axis) in the intensively (◆) and conventionally (●) treated groups in the United Kingdom Prospective Diabetes Study (redrawn from reference 1). The aim of treatment in the conventionally treated group was to achieve a fasting plasma glucose <15 mmol/l and/or to abolish symptoms of hyperglycaemia, whereas in the intensively treated group the aim was to achieve a fasting plasma glucose <6 mmol/l.[1]

Patients and physicians need to be aware that patients are likely to need the addition of other therapeutic agents at regular intervals[1] and those with diabetes should be made aware at an early stage that the need for such augmentation does not represent 'failure' on their part, nor an unexpected outcome. Physicians should avoid becoming complicit in an attempt to belittle type 2 diabetes in its early stages as a 'minor condition' which can 'easily be managed' by diet and tablets. Such an introduction to diabetes leads to later disappointment or self-reproach.

Attempting to avoid polypharmacy or insulin treatment

Patients and physicians have often colluded in implicit and unspoken contracts to continue oral agents for as long as possible. Physicians prevaricate with a view that they are giving improvement of diet or another effort at weight-loss one last chance. Patients adopt optimistic views based on lack of symptoms or have pragmatic fears about the complexity of insulin. Some patients even regard insulin therapy as a prelude to death—the medical equivalent of the last rites.

Patients' fears and medical reluctance need to be overcome if appropriate therapy is to be delivered and the complications of diabetes avoided.

It is clear from the UKPDS[1] that many patients will require multiple drug regimens, as well as an escalation of dose over the years of their treatment. This therapeutic plan needs to be explained early in the course of type 2 diabetes so that patients and physicians alike can discuss realistic glycaemic goals.

Avoiding hypoglycaemia

In the DCCT, intensive treatment was accompanied by a threefold increase in rate of hypoglycaemia ($p<0.001$): 27% of patients in the intensively treated group experienced at least one episode of severe hypoglycaemia during the first year compared to 10% in the conventionally treated group.[11] However, the high rates of hypoglycaemia in type 1 diabetes observed in the DCCT are not relevant to type 2 diabetes. The UKPDS[1] intensively-treated group showed a 2.3% annual incidence of severe hypoglycaemia (requiring help from another person) in those on insulin and a much lower percentage rate for those on oral agents (Figure 2).

Although the increased potential for hypoglycaemic episodes with intensive treatment may limit

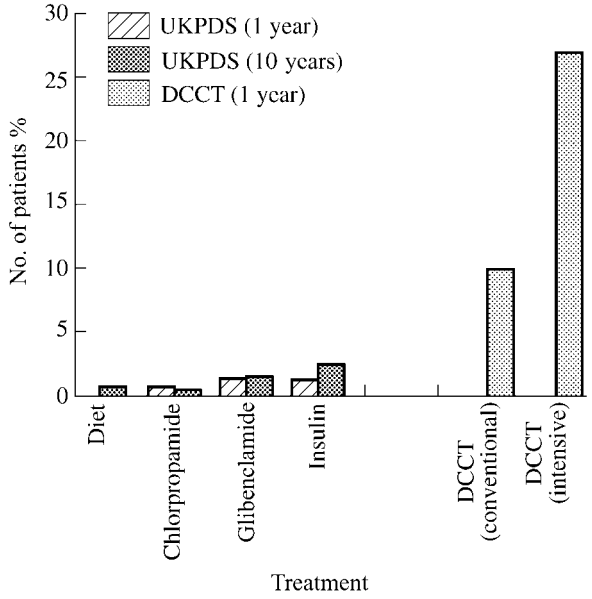

Figure 2. The number of patients experiencing severe hypoglycaemic episodes (i.e. necessitating assistance from another person) per year in the intensively treated group in the United Kingdom Prospective Diabetes Study at one and ten years in subjects taking chlorpropramide, glibenclamide, insulin or on diet alone; and in the Diabetes Control and Complications Trial in 711 intensively treated patients and 730 conventionally treated patients at one year.[1,11]

the degree of control attainable, this should not deter clinicians and patients from attempting to achieve tighter control. Appropriate oral therapy can minimize hypoglycaemia (glibenclamide caused more hypoglycaemia than chlorpropramide, and metformin less than any sulphonylurea). There is no inherent reason why clinicians should be prepared for some hypoglycaemia episodes in type 1 diabetes and not in type 2—the aim of therapy is the same, namely to avoid complications by appropriate glycaemic management.

Concern over the possibility of increased macrovascular risk

Concern over the risk of atherogenicity due to high doses of insulin

Many type 2 diabetic patients are overweight[1] and insulin-resistant[12] and so they may require high doses of insulin. This has led to concerns about possible atherogenic effects of insulin.[13] The UKPDS showed no increase in myocardial infarction rates in the intensively treated group, and no difference in macrovascular endpoints between the intensively and conventionally treated groups. A 16% risk reduction in myocardial infarction with intensive treatment was of borderline significance ($p=0.052$), although this may reflect the relatively short follow-up of 10 years, compared to the median life expectancy, at diagnosis, of 20 years (1). This raises the possibility of seeing a significant benefit if patients are followed-up for longer. The benefits conferred by good control outweigh any theoretical and unsubstantiated disadvantages.

Concern over adverse cardiovascular effects from sulphonylureas

Despite previous concerns about the possibility of tolbutamide playing a role in preventing ischaemic preconditioning,[3] the UKPDS did not show any deleterious effect of sulphonylureas on macrovascular end-points.[1]

Imprecise guidelines

There is a wide degree of variation between the various HbA1c assays currently in use, resulting in differing numerical goals at different centres which in turn leads to confused or confusing guidelines. The variation in HbA1c across 100 laboratories in the UK is shown in Figure 3. This variation should not be the basis for mismanagement of patients, and local guidelines can be 'corrected' to the candidate reference method used in the DCCT as part of the US National Glycohaemoglobin Standardization Program. Replication of the UKPDS results would involve measuring fasting plasma glucose at 3-month intervals, and adjusting therapy aiming to achieve a value of $\leqslant 6$ mmol/l. The 'achieved' HbA1c of the UKPDS intensive policy group was not the 'aim'. Indeed, by definition, 50% of patients had values below the median. One would have to aim,

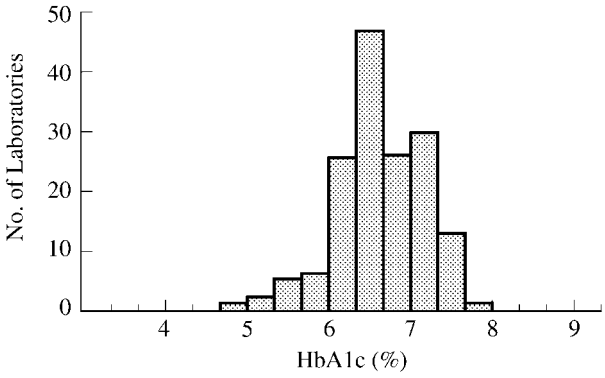

Figure 3. Results of HbA1c assays (*x*-axis) performed in 100 laboratories in the UK, against the number of laboratories producing each numerical result (*y*-axis) compared to a target HbA1c of 6.3%. From the UK National Quality Assurance Scheme for haemoglobins, September 1998. Reproduced with permission from Dr D. Bullock.

generally, lower than the median value if one were to achieve this goal in clinical practice. A pragmatic view should prevail: that any improvement of glycaemia towards the normal levels is likely to reduce the risk of complications.

Weight gain

Many type 2 diabetic patients are overweight at diagnosis; the mean body mass index of patients at entry to the UKPDS was 27.5 kg/m^2,[1] and patients are worried about the role insulin therapy may play in causing further weight gain. Doctors are concerned about the risk of setting up a vicious circle of increasing weight and increasing insulin resistance with consequent deterioration in glycaemic control and escalation of insulin doses.

Patients assigned to intensive treatment gained a mean of 3 kg more than those assigned to conventional treatment after 10 years: patients treated with insulin gained 4.0 kg more, those on chlorpropamide gained 2.6 kg more, and those assigned to glibenclamide gained 1.7 kg more than those in the conventional treatment group[1] (Figure 4). Intensive treatment is associated on average with weight gain, and patients and physicians need to address the problem proactively. Patients should be told to reduce their insulin if they get recurrent hypoglycaemia rather than increase food intake: snacks should be discouraged in those on long-acting insulin alone, and additional dietetic advice about reduction of total calorie intake may be necessary.

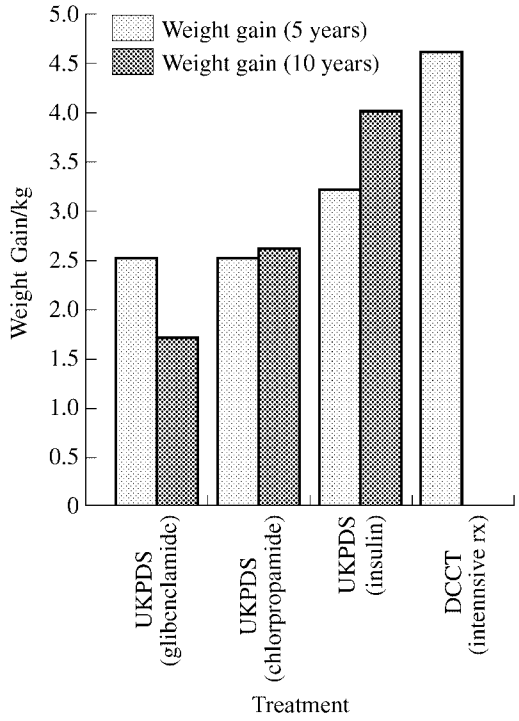

Figure 4. The excess weight gain occurring with any form of intensive treatment in subjects with type 2 diabetes taking glibenclamide, chlorpropramide or insulin in the United Kingdom Prospective Diabetes Study at 5 and 10 years; and in patients with type 1 diabetes receiving insulin three or more times daily by injection or an external pump in the Diabetes Control and Complications Trial at five years.[1,4]

However, notwithstanding the weight gain in the UKPDS patients, there was still a lower complication rate with intensive treatment: of the two risks, weight gain is less dangerous than chronic hyperglycaemia.

Limitations of current technology

Although many patients find it much easier to inject insulin using a pen device, at present the maximum single dose delivered by a pen system is limited to 70 units. As many patients with type 2 diabetes are overweight and insulin-resistant, they may well require doses in excess of 70 units, and the current limitations in technology should not deter physicians and patients from increasing insulin doses beyond 70 units as required. Higher doses can be delivered by dialling the dose in two stages or using vials and syringes. Physicians tend to become over-cautious in the use of insulin in doses >100 units/day, but insulin resistance generally prevents rapid swings of glycaemia, and hypoglycaemia in such patients is very rare.

The elderly

There are some caveats to the use of insulin: elderly patients may find the technology difficult, and failing eyesight and dexterity need to be taken into consideration. On the other hand, it is ironic that some old people will have failing eyesight simply *because* they were not appropriately treated with insulin. Physicians should be cautious of the ageist view of the elderly as frail, untrainable and liable to deteriorate in any event.

Unintentional non-compliance

Several studies have shown that admissions due to unintentional non-compliance occur with twice the frequency in the elderly (19%) compared to the general population (10%).[14,15] Factors contributing to non-compliance include confusion regarding the drug regimen in 28.4% of patients, fear of side-effects in 19.4%, and forgetfulness in 16.4%.[16] The elderly may require greater educational input than their younger counterparts to overcome inadvertent non-compliance.

Physical factors/impediments

Poor manual dexterity can result in difficulty in taking medication: the ease with which the elderly manage to open different drug containers varies considerably, from 89.95% managing to open a blister pack to only 36.9% managing to open a child-proof container. The inability to handle drug containers correctly correlates with vision, cognitive capacity and manual dexterity.[16] Many older patients may find it difficult to manage home blood glucose monitoring and injections, due to poor sight or reduced manual dexterity control, and will therefore require additional specialist input to help select the most appropriate glucose meter and injection device.

Resources

Intensifying treatment in patients with type 2 diabetes will require an initial increase in resources in terms of drug costs and nursing and medical input in the short term. Although the median daily insulin dose at 12 years in UKPDS was 36 units of insulin, this figure is an underestimate of the doses needed in clinical practice, as in the study people with good control were randomized to insulin and therefore required lower doses than those patients started on insulin for poor glycaemic control. The annual cost of a daily dose of 62 units (which represents the mean daily dose of insulin in patients with type 2 diabetes in our clinic), of Mixtard 30 compared to the annual cost of a combination of metformin 1.5 g and gliclazide 320 mg is shown in Figure 5.

In the long term, this increase in expenditure will be at least partly offset by the reduction in complications needing treatment. For example the need for cataract extraction was reduced by 24% ($p=0.046$) and the need for photocoagulation by 29% ($p=0.0031$) in the patients allocated to intensive treatment in the UKPDS. The number needed to treat to prevent one person from developing a single endpoint event over 10 years was 19.6 (95% CI 10–500).[1]

Conclusion

There are a multiplicity of reasons for suboptimal glycaemia in type 2 diabetes, including a lack of appreciation of the progressive decline in β-cell failure in conjunction with misguided attempts to avoid polypharmacy or insulin therapy. Concerns regarding the risk of hypoglycaemia and of exacerbating weight gain, and unfounded fears over the possibility of increased macrovascular risk with insulin therapy also contribute to the problem. Additional factors include the existence of imprecise guidelines

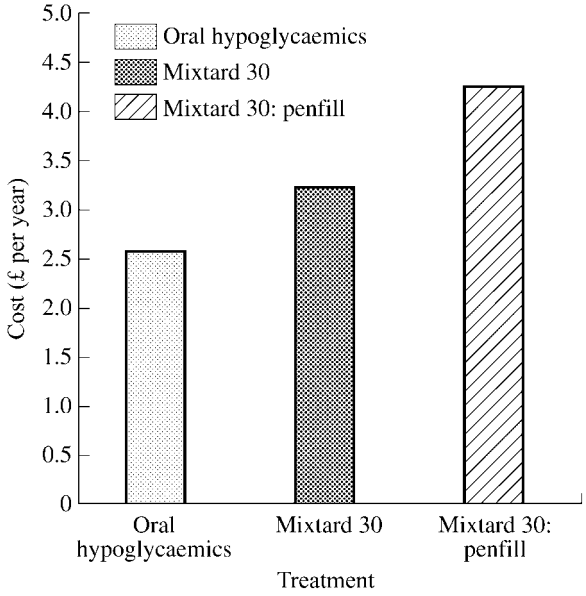

Figure 5. The annual cost of treatment in £ sterling of Mixtard 30 (62 units daily) in vials and penfills and the combination of metformin (1.5 g daily) with gliclazide (320 mg daily).

and treatment targets, limitations in currently available technology, ageist policies, and a lack of resources.

However the glycaemic objectives in type 2 diabetes should not differ from those in Type 1 diabetes, namely to aim to normalize glycaemia and HbA1c, minimize the risk of hypoglycaemia and avoid adversely affecting quality of life.

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