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Overcoming the hurdles to achieving glycemic control

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Abstract

Several factors influence diabetes control, and many of these can adversely affect endeavors to obtain optimal glycemic management. For many patients with type 2 diabetes mellitus, the passage of time often results in a loss of responsiveness to medication and a greater difficulty in achieving desired target levels. Although these observations in part reflect a natural progression of diabetes, irrespective of treatment given, it is possible to identify modifiable hurdles that can be addressed with better outcome results. Lifestyle measures, particularly diet and exercise, remain paramount, whereas other secondary confounding factors such as systemic or endocrine disease or other conflicting medication need specific therapeutic attention. Most patients with type 2 diabetes mellitus will require oral hypoglycemic medication and this should be prescribed in the simplest, most effective, and safest way. Ensuring that patients fully understand treatment objectives is important resulting in better compliance with advised treatment. Such compliance can be significantly improved by keeping treatment regimens simple. With its novel once-daily formulation, gliclazide modified release has been shown to improve adherence to medication and result in better glycemic outcome as determined by improved HbA_{1c} levels. Its benefits in terms of reduced risk of hypoglycemia have been demonstrated in the GlUcose control In type 2 diabetes: Diamicron modified release versus glimEpiride study.

1. Introduction

The evidence based from recent published studies, particularly the United Kingdom Prospective Diabetes Study, has indicated that aggressive treatment of hyperglycemia to a defined target (suggested HbA_{1c} <7%) should significantly reduce the risk of development and progression of microangiopathic complications in type 2 diabetes mellitus (T2DM) [1]. In the clinical practice setting, a target level of glycemic control as determined by HbA_{1c} <7% may not be easily achieved with a substantial 50% proportion of patients failing to meet this given target, increasing to fewer than 25% after 9 years of therapy [2]. As a result, it has been argued that targets should be both realistic and practical for routine clinical care [3]. Determining the barriers to achieving optimal glycemic control is therefore important in enabling patients to do better in terms of improving diabetes control and thereby reducing risk of longer-term complications.

2. Pathogenesis of T2DM

A wide spectrum of interrelated variables that influence diabetes control can be identified, ranging from the heterogeneous and progressive nature of T2DM itself to the many different lifestyle and behavioral factors that are encountered in everyday living with diabetes. T2DM comprises differing degrees of the bipolar disturbance of beta-cell dysfunction and insulin resistance, both of which significantly determine response to prescribed therapy. The capacity of the beta cell to maintain adequate insulin secretion is fundamental for effective responsiveness to oral hypoglycemic agents, whereas insulin resistance, usually related to obesity, puts greater demand on beta-cell insulin secretory reserve. Both reduced beta-cell function and increased insulin resistance are major adverse contributory factors to achieving good therapeutic outcomes.

With the passage of time, T2DM progresses and beta-cell responsiveness diminishes at differing rates between individuals. The United Kingdom Prospective Diabetes Study, using the homeostatic model assessment, observed an approximate 4% to 5% per annum decline in beta-cell function irrespective of all treatment given [4]. The effect was similar for various treatment interventions with comparable outcomes for insulin, sulfonylureas, and metformin, all

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Table 1
Adverse effects of therapies for T2DM

Biguanides	Gastrointestinal intolerance, lactic acidosis, malabsorption
Sulfonylureas	Hypoglycemia, weight gain
Thiazolidinediones	Fluid retention (increased risk of heart failure), weight gain, anemia
α-Glucosidase inhibitors	Gastrointestinal intolerance
Insulins	Hypoglycemia, weight gain, injection site problems

of which did better than diet alone in terms of goal attainment by 9 years' duration, and with no indication that sulfonylureas accelerated the process.

3. Adverse drug effects

The occurrence of drug-associated side effects is known to be a significant hurdle. No current treatment is without potential side effects and these will be familiar to the prescriber (Table 1). Such side effects are usually specific to the individual drug concerned, but patients vary considerably in the way they react to drugs. Of the drugs commonly used for glycemic control, biguanides (metformin) are associated with a relatively high frequency of gastrointestinal adverse reactions and rarely lactic acidosis; similarly, α-glucosidase inhibitors (acarbose) cause gut side effects; thiazolidinediones (rosiglitazone, pioglitazone) can be associated with weight gain, fluid retention, increased risk of heart failure, and occasionally anemia. Sulfonylurea agents have the potential to cause weight gain and hypoglycemia, but with significant differences within the class dependent on the pharmacodynamic insulin response to the particular sulfonylurea agent given. Insulin itself is not without side effects and, apart from the need for injection, also has the propensity to cause weight gain and serious hypoglycemia.

Type 2 diabetes mellitus is characterized by blunting of first-phase insulin secretion. Although sulfonylurea agents improve the insulin secretory response to hyperglycemia, individual differences occur between the different sulfonylureas themselves. Prolonged and inappropriate second-phase insulin stimulation, as seen with glibenclamide, is more likely to cause hypoglycemia and weight gain. In contrast, sulfonylurea agents such as gliclazide modified release (MR) [5], which predominantly influence first-phase insulin secretion, are less likely to be associated with these side effects.

This difference may have implications in respect of beta-cell protection. In a 20-year retrospective study, Satoh et al [6] observed that patients treated with gliclazide continued for a longer period before the need for insulin initiation with a mean duration of 14.5 years compared with patients on glibenclamide with a mean duration of 8 years (Fig. 1). Gliclazide-treated patients had lower HbA_{1c} levels (6.8% vs 7.4% on glibenclamide), and so the results may in part relate to reduced glucose toxicity. However, even when adjusted for the difference in HbA_{1c}, the use of gliclazide remained an independent factor. Therefore, other differences, such as the reduced oxidative stress as reported with gliclazide [7], may also have determined the significantly longer period without the need for starting insulin.

4. Confounding factors

Attention to lifestyle considerations cannot be overemphasized. Poor diet, inadequate physical activity, and obesity represent a triad of adverse factors that contribute to the development of T2DM and confound attempts to secure good diabetes control. Cigarette smoking and high alcohol consumption are other counterproductive and detrimental lifestyle habits that greatly increase risk of long-term complications.

Other concomitant disease may result in secondary aggravation of glycemic control. Systemic illness of an acute, chronic, or inflammatory nature has the potential to exacerbate hyperglycemia and should be treated specifically. Other endocrine disorders, particularly with overproduction of insulin antagonistic hormones such as growth hormone, cortisol, or thyroxine, need separate therapeutic

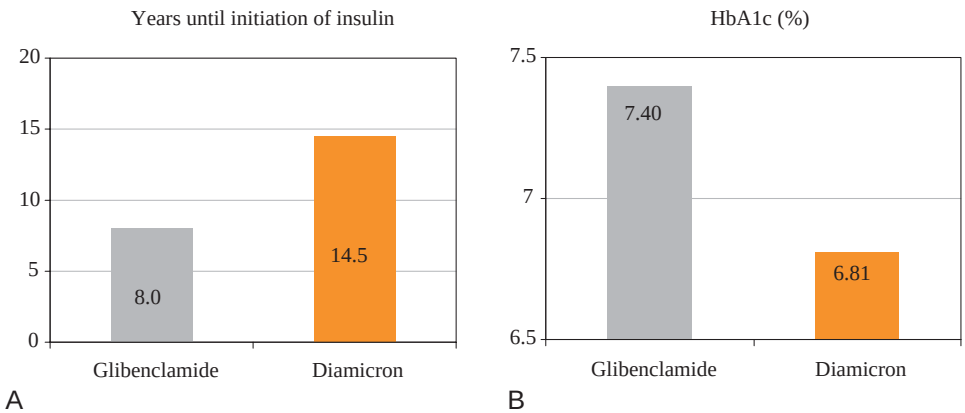

Fig. 1. A, Duration until initiation of insulin from start of gliclazide or glibenclamide treatment ($P < .0001$). B, Mean HbA_{1c} (%) until insulin from start of gliclazide or glibenclamide ($P < .0001$).

consideration. Certain medications may also be conflicting, such as steroids, thiazides, and antipsychotics. When detected, it is important to address these other confounding factors as part of overall therapeutic management.

Patient attitudes and beliefs will also determine response to treatment regimens. In the study of perceptions and experiences of taking oral hypoglycemic agents, Lawton et al [8] identified 4 key factors that may influence outcome: confidence in the advising health care professional; perception of the efficacy of prescribed medication; expectations of benefit; and beliefs concerning possible detrimental effects. Recognizing that these issues can provide a barrier to success, Greenhalgh [9] in an accompanying commentary underlined the essential need for good communication between the patient and the health care professional, to ensure adequate information is given with open discussion in sufficient time, so that intended treatment objectives are understood and that the wishes of the patient are respected as a genuine informed choice.

5. Compliance considerations

Taking tablets as recommended is not always easily achieved, and failure to do so will result in a suboptimal response. In a prospective assessment of self-reported compliance of more than 11 000 patients with T2DM, Guillausseau [10] observed optimal adherence to prescribed therapy in only 46% of patients. However, differences occurred depending on the frequency that tablets were administered. Low daily dosing was associated with better compliance and better HbA_{1c} levels: with tablets taken once daily, compliance was greatest at 60%; with twice daily 45% and with 3 times daily, only 40%. The frequency of dose taking was significantly linked to the HbA_{1c} result: once daily HbA_{1c}, 7.0%; twice daily, 7.3%; 3 times daily, 7.7% (Fig. 2). Guillausseau also showed that missing medication was adversely linked to HbA_{1c} outcome with highest HbA_{1c} levels observed in those where medication was missed more regularly. A study extension [11] found that changing from multiple daily sulfonylurea usage to once-daily dosage with gliclazide MR increased compliance from 44% to 69.5% and lowered the HbA_{1c} from 7.5% to 6.9%.

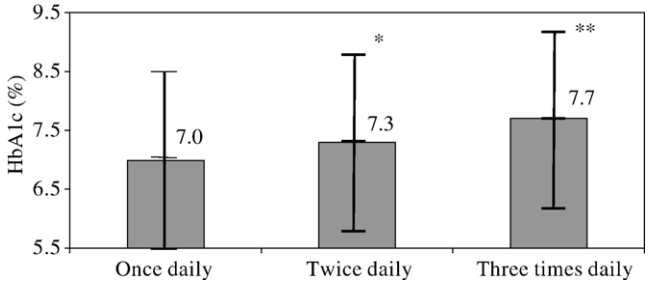

Fig. 2. Glycated hemoglobin (HbA_{1c}) levels (%) in type 2 diabetic patients according to the frequency of daily doses of antidiabetic oral agents. *$P < .05$; **$P < .01$ vs once-daily dosing.

Table 2
Mean values of glycated hemoglobin (HbA_{1c}) in studied groups (efficacy set)

Group	HbA_{1c} level (%)			
	Baseline	Week 8	Week 16	Δ Week 16 − baseline***
Gliclazide MR	6.9 ± 1.0	6.5 ± 1.3	6.4 ± 1.6	−0.5 ± 1.3**
Glibenclamide	7.2 ± 1.1	7.4 ± 1.4	7.6 ± 1.3	0.4 ± 1.2*

* $P = .0014$, within group (week 16 − baseline).
** $P = .0006$, within group (week 16 − baseline).
*** $P < .0001$, between group (gliclazide MR vs glibenclamide).

A further compliance study (DIACOM [Effect of DosIng frequency of oral Antidiabetic agents on the COMpliance and biochemical control of type 2 diabetes]) by Kardas [12] in respect of dose frequency of oral hypoglycemic agents used a novel electronic monitoring system known as the Medication Event Monitoring System by means of an electronic microprocessor inserted into the cap of the bottle containing the tablets. This permitted registering the date and time of every opening and was able to determine the correct number of doses and timing of medication as well as the number of missed/delayed doses. The observed results were also backed up by a standard pill count. After a run-in period, patients previously on glibenclamide were randomized either to continue on glibenclamide twice daily or to switch to gliclazide MR once daily at equivalent doses. One hundred five patients were randomized, and efficacy data were available for 99 and compliance data for 97 patients (49 gliclazide, 48 glibenclamide). There was an overall 90.4% compliance with medication, but significant differences were observed between the 2 therapies: 93.5% compliance for gliclazide MR, 87.2% for glibenclamide. After 16 weeks' therapy, these differences were also associated in terms of glycemic outcome. The fasting blood glucose level improved by 18.9 mg/dL with gliclazide MR and by 3.0 mg/dL for glibenclamide. This was also reflected in changes in HbA_{1c} levels; with gliclazide MR the HbA_{1c}

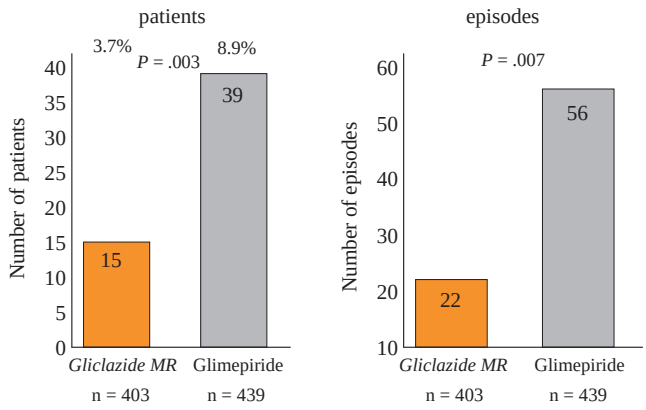

Fig. 3. Number of patients having an episode and total number of hypoglycemic episodes with blood glucose of less than 3 mmol/L according to gliclazide MR or glimepiride treatment in the GUIDE study (no hypoglycemia required external assistance).

fell from 6.9% to 6.4%, whereas with glibenclamide the level rose from 7.2% to 7.6% (Table 2). The DIACOM study would indicate that a reduced daily frequency of medication is associated with better compliance and better glycemic control.

While improving adherence to medication by simplifying treatment regimens with single daily tablet dosing, reducing drug side effects will also result in better compliance and better outcomes. The GlUcose control In type 2 diabetes: Diamicron modified release versus glimEpiride (GUIDE) study compared the novel formulation of gliclazide MR with glimepiride, either as monotherapy or in combination with other oral hypoglycemic agents [13]. After randomization to either gliclazide MR or glimepiride, patients entered a 27-week double-blind treatment period that comprised a 9-week titration period with dose adjustment every 3 weeks until metabolic control was achieved (therapeutic goal defined as fasting plasma glucose of 5-7.8 mmol/L), followed by an 18-week maintenance period. A discretionary increase in glimepiride to 6 mg was permitted at week 18 review to ensure adequate use of all available doses of sulfonylurea.

Eight hundred forty-five patients were randomized in the study. In terms of glycemic efficacy, the outcome for both gliclazide MR and glimepiride was similar and comparable, with both agents showing an approximate 1.0% reduction in HbA_{1c} level. At the end of the study, 50% of patients achieved an HbA_{1c} of less than 7% and 25% an HbA_{1c} of less than 6.5%. A major component of the GUIDE study was to examine the incidence of hypoglycemic episodes, specifically assessed using the classification of the European Agency for Evaluation of Medicinal Products, which determines 3 categories of hypoglycemia: (1) severe symptoms + external assistance + blood glucose of less than 3 mmol/L; (2) blood glucose of less than 3 mmol/L ± symptoms; and (3) suggested symptoms alone. Blood glucose measurement was obtained for 68% of all symptomatic events. No major hypoglycemic episodes occurred, but there were significant differences between the 2 groups in respect of the frequency of hypoglycemia with blood glucose of less than 3 mmol/L with or without symptoms, with 50% fewer hypoglycemic events in the gliclazide MR group compared with those on glimepiride (Fig. 3). The occurrence of hypoglycemia was evenly distributed across the 27-week period. Hypoglycemia tended to occur at a lower dosage of both medications and it was observed that gliclazide MR was associated with less hypoglycemia at lower HbA_{1c} concentration, allowing the potential for more aggressive therapy to target. Other adverse effects were not a problem during the study and no other significant differences were observed between the 2 groups. Both gliclazide MR and glimepiride were essentially weight neutral with no observed differences between the 2 agents and body weight remaining stable.

In conclusion, when endeavoring to overcome the difficulties and hurdles to achieving good glycemic control, a number of different issues can be identified that need to be addressed. These can be summarized as follows:

- To identify confounding factors and ameliorate such where possible.
- To improve patient education and to enable informed choice and sharing of treatment goals.
- To advise the simplest, most effective, and safest medication that promotes compliance and achieves desirable outcome.

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