HbA_{1c} Reduction with Basal Insulin in Type 2 Diabetes Mellitus

a report by
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Type 2 diabetes is a growing health problem that is generating ever-increasing morbidity and economic consequences. Individuals with type 2 diabetes face insulin resistance coupled with a progressive loss of insulin production by their β cells, meaning that there is an inevitable need for replacement insulin as the disease progresses. As the age of onset of type 2 diabetes is decreasing due to a variety of lifestyle factors, the burden of long-term micro- and macrovascular complications is increasing.[1,2] Randomised trials with long-term follow-up such as the United Kingdom Prospective Diabetes Study (UKPDS) provide strong evidence that reducing glycated haemaglobin (HbA_{1c}) improves long-term prognosis in terms of microvascular complications; however, the impact of improved glycaemic control on macrovascular complications is less clear.[3] Another randomised trial with long-term follow-up (the Steno Diabetes Centre's 'Steno-2' trial) shows that glucose control combined with aggressive interventions to deal with other cardiovascular (CV) risk factors can reduce CV disease by 50% in patients with type 2 diabetes.[4]

Although good glycaemic control improves long-term prognosis, the reality is that most patients are in poor control.[5] To a large extent this reflects a delayed use of insulin. There are a number of barriers to the initiation of insulin, particularly in the attitudes and perceptions of both patients and their care-givers. These attitudes include: concern about further complicating an already complex treatment programme; fear of hypoglycaemia; fear of weight gain (in patients who are already typically overweight); and fear of injections.[6] Physicians and diabetes educators have an important role in reassuring patients during this transition stage. If they and their patients see insulin initiation as a necessary step in the treatment of a progressive disease, and not as a sign of failure to achieve adequate glycaemic control with the aid of oral antidiabetic drugs (OADs), the transition to insulin should be easier.[7] In addition, once patients initiate insulin they tend to report an improved quality of life.[8,9] Therefore, a widely held paradigm is that insulin needs to be introduced using a simple and acceptable regimen to overcome any barriers to initiation. With the increasing prevalence of type 2 diabetes it is likely that primary care-givers rather than diabetologists will need to take greater responsibility for initiating insulin. This should also increase the attractiveness of a simple yet effective regimen.

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Insulin Initiation

The simplest and safest way to initiate insulin is to supplement oral therapy with a once-daily (OD) injection of basal insulin. Primarily, this approach lowers fasting blood glucose (FBG) and total glucose load. These are effective first steps, particularly in patients with clearly elevated HbA_{1c}.[10] Although this does not directly address the increasingly blunted prandial insulin response in type 2 diabetes observed in the setting of residual β-cell function, it could afford β cells rest and relieve glucotoxicity, thereby facilitating a partial recovery of physiological insulin responses. In support of this, early insulin initiation resulted in improved fasting endogenous insulin secretion following treatment withdrawal after two years compared with individuals who received sulphonylurea treatment.[11] A four-year follow-up also demonstrated that early insulin initiation resulted in improved endogenous insulin secretion during the first two years and superior HbA_{1c} control in years two to four compared with individuals treated with sulphonylureas, suggesting long-term benefits of early insulin treatment.[12]

In the past, basal insulins were suboptimal in terms of their pharmacokinetic profiles. For example, the peaked absorption profile of neutral protamine Hagedorn insulin (NPH) was known to be capable of precipitating nocturnal hypoglycaemic episodes if titrated too aggressively in pursuit of a strict fasting glucose target.[13,14] In fact, concerns about hypoglycaemic events in type 2 diabetes are often exaggerated, especially with basal insulins, as these patients tend to be insulin-resistant and the absolute event rates are low (approximately 10% of the rates observed in individuals with type 1 diabetes).[15] In addition, there were no significant differences in rates of mild or severe hypoglycaemic events in patients with type 2 diabetes whether they were treated with insulin or a sulphonylurea.[15] Nevertheless, in this often older population nocturnal hypoglycaemia is to be avoided when possible. A significant reduction in total, daytime and nocturnal hypoglycaemic episodes was reported in individuals who were previously treated with OADs alone, insulin glargine plus OADs or NPH plus OADs following their

Table 1: Treat-to-target Trials of Basal Insulin Analogues in Insulin-naïve Patients with Type 2 Diabetes

Author (Ref)	Insulin	HbA_{1c} (%) Baseline	HbA_{1c} (%) End	FPG (mmol/l) Baseline	FPG (mmol/l) End	Hypoglycaemia RR	Weight Gain (kg)
Riddle et al., 2003[17]	Glargine pm	8.6	7.0	11.0	6.5	0.79	3.0
	NPH pm	8.6	7.0	10.8	6.7		2.8
Hermansen, 2006[18]	Detemir BID	8.6	6.8	11.1	6.9	0.53[a]	1.2[a]
	NPH BID	8.5	6.6	10.8	6.6		2.8
Philis-Tsimikas, 2006[19]	Detemir am	9.1	7.5	11.5	8.6	0.68	1.2
	Detemir pm	8.9	7.4	10.8	7.2	0.47[a]	0.7[b]
	NPH pm	9.2	7.4	11.5	7.8		1.6
Holman, 2007[23]	Detemir pm or BID	8.4	7.6	9.5	6.2	RR not reported	1.9[a]
	Biphasic BID	8.6	7.3	9.7	7.2		4.7[c]
	Prandial TID	8.6	7.2	9.6	8.3		5.7
Rosenstock, 2007[26]	Detemir pm or BID	8.6	7.2	10.8	7.1	0.94	3.0[b]
	Glargine OD	8.6	7.1	10.8	7.0		3.9

Between-treatment comparison: [a] p<0.001; [b] p<0.01; [c] p<0.005.
RR = relative risk; OD = once daily; BID = twice daily; TID = three times daily.

transition to insulin detemir plus OADs.[16] Therefore, increased hypoglycaemia should not be of major concern to patients transitioning to basal insulin.

The basal insulin analogues (detemir and glargine) have a flatter, longer and more predictable blood glucose (BG)-lowering profile than NPH.[13,14] Their OD utility and entry into a clinical setting of increasing type 2 diabetes, tightening guidelines on glycaemic targets and pressure for primary care insulin initiation have revitalised interest in and research into the tactic of basal insulin as a start-up regimen.

Basal plus Oral Therapy – Results from Clinical Studies

The era of OD basal insulin was fully established by a treat-to-target (TTT) trial of insulin glargine versus NPH showing that with an aggressive insulin titration algorithm, clinically important improvements of 1.6% can be made in HbA_{1c} with a simple basal insulin regimen (see *Table 1*).[17] In this trial 57–58% of patients treated with glargine and NPH achieved HbA_{1c} levels ≤7.0%; however, there were slightly but significantly fewer hypoglycaemic episodes with glargine (13.9 versus 17.7 symptomatic hypoglycaemic events/patient-year, respectively; p<0.02). The first TTT trial with insulin detemir using a similar titration algorithm, by Hermansen et al., gave even better results, with 70% of individuals in both arms reaching the target HbA_{1c} level of ≤7.0%, albeit with a twice-daily (BID) schedule (see *Table 1*).[18] In addition, detemir reduced rates of all hypoglycaemic events and nocturnal hypoglycaemic events by 47 and 55%, respectively, compared with NPH (p<0.001).[18] Mean weight gain was also significantly less with detemir compared with NPH (1.2 versus 2.8kg; respectively, p<0.001) (see *Table 1*). Subsequently, Philis-Tsimikas et al. showed a similar level of HbA_{1c} reduction using OD detemir compared with the other TTT trials (mean 1.5% HbA_{1c} reduction for OD evening detemir) in patients with a higher baseline HbA_{1c} compared with patients in the other TTT trials (9.1% in the Philis-Tsimikas et al. trial,[19] 8.6% in the Riddle et al.[17] and Hermansen et al.[18] trials). In addition, the Philis-Tsimikas trial confirmed the hypoglycaemia and weight advantages of detemir compared with NPH.[19]

Studies suggest that BID dosing tends, on average, to escalate the insulin dose without achieving a proportional improvement in glycaemic control.[20] There is also evidence that as HbA_{1c} declines, post-prandial hyperglycaemia gains importance in terms of overall contribution to residual hyperglycaemia.[10,21] This may explain why increasing the basal insulin dose through BID dosing does not have a proportional effect on reducing HbA_{1c}. By reviewing the available data, DeVries et al. have also suggested that the level of HbA_{1c} reduction achievable with basal insulins using a TTT approach is ~1.5%, regardless of baseline level.[20] HbA_{1c} reductions of 1.99 and 2.1% were observed in a TTT trial of glargine plus metformin or NPH plus metformin, respectively, reflecting the aggressive fasting BG target of 4.0–5.5mmol/l.[22] This again suggests that simple basal plus oral therapy can result in appreciable improvements in HbA_{1c}. Therefore, bringing these data together provides support for the early initiation of OD basal insulin treatment in order to achieve glycaemic targets, and for the addition of mealtime insulin rather than BID basal insulin if HbA_{1c} fails to meet targets.

The need for early insulin initiation is also supported by the Treating-To-Target in Type 2 diabetes (4-T) study.[23] The study demonstrated that OD insulin detemir and BID biphasic insulin aspart were comparable in terms of the likelihood of achieving HbA_{1c} values of ≤6.5% in individuals with baseline HbA_{1c} <8.5%, although detemir offered advantages in terms of weight gain (1.9kg for basal and 4.7kg for biphasic insulin; p<0.001) and hypoglycaemia (2.3 versus 5.7 events/patient-year). However, in patients with HbA_{1c} levels >8.5%, the biphasic insulin offered an increased likelihood that patients would achieve an HbA_{1c} ≤6.5% (odds ratio for the basal group 0.21; 95% confidence interval (CI) 0.07–0.65; p=0.007). In the 4-T study, the overall HbA_{1c} reduction observed with basal insulin was lower than those observed in the earlier TTT trials (0.8% in 4-T versus 1.4–1.8% in the other TTT trials). This may reflect the fact that the patient–carer contact rate was much reduced in the 4-T study compared with the earlier TTT trials.

Therefore, this last observation raises the concern that the rather intensive TTT trials may overestimate the outcomes that are achievable in the 'real world', where patients do not receive such close clinical support. However, the Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVE™) observational study, which is examining the empirical use of detemir in an everyday clinical setting, shows that important HbA_{1c} reductions are still achievable with basal plus oral therapy.[16] For example, in the German cohort of the PREDICTIVE™ trial, patients with type 2 diabetes treated with OADs

alone, NPH plus OADs or glargine plus OADs were transferred to insulin detemir plus OADs and followed up for 12 weeks.[16] HbA_{1c} improved by ~1.3% in previously insulin-naïve patients, and by ~0.6% in patients switched from alternative basal insulin plus OAD regimens ($p<0.0001$ for all cases).[16] In addition, total, daytime and nocturnal hypoglycaemic events declined by more than 80% from baseline – even in previously insulin-naïve patients.[16] Encouragingly, therapy with insulin detemir treatment was not associated with weight gain, with a mean loss of 0.9kg during the 12-week study across these subgroups.[16] In this study, 79% of patients used OD insulin detemir, underlining the fact that insulin detemir should generally be used OD in type 2 diabetes.[16]

Insulin glargine has been studied prospectively in an outpatient setting in A Trial comparing Lantus® Algorithms to Achieve Normal blood Glucose Targets in Patients with Uncontrolled blood Sugar (AT. LANTUS), which was designed to compare two titration algorithms.[24] In this study, the cohorts combined insulin-naïve and previously insulin-treated patients, and the use of prandial insulin was permitted. These factors confound interpretation of results. A recent report involving a UK subgroup from AT.LANTUS, of which 38% were insulin-naïve, compared outcomes in patients managed from primary and secondary care settings.[25] Hypoglycaemia occurred infrequently and there were significant decreases in HbA_{1c} of ~0.5 and 1.0%, respectively (from different baseline values), with modest weight gains of 1.0 and 1.2kg, respectively. Although the reduction in HbA_{1c} in the primary care setting may appear relatively low in this study, this may reflect the more limited scope for improvement that is possible when a high percentage of the cohort has already been receiving an alternative insulin regimen. The authors noted a relative reluctance in the primary care setting to intensify the regimen by titrating prandial insulins at mealtimes.

Conclusions

Basal plus oral therapy with insulin analogues can achieve excellent results in terms of improved glycaemic control with minimal risk of hypoglycaemic events in type 2 diabetes patients. In addition, once-daily insulin detemir can help these patients to avoid excessive weight gain. This is particularly beneficial as patients with type 2 diabetes are often overweight at insulin initiation. The efficacy and tolerability of basal plus oral therapy with insulin analogues has been demonstrated both in the rigorously controlled setting of TTT trials and the 'real life' setting of large observational studies or studies in a primary care setting. With the weight of evidence supporting the early initiation of insulin therapy for improved long-term outcomes, basal plus oral therapy offers a simple, tolerable and acceptable regimen that can help both patients and healthcare workers to overcome their perceived barriers to insulin initiation. Once patients start insulin therapy, they generally appreciate the quality of life benefits that it provides and may become more open to additional therapies as their diabetes progresses. In terms of optimising basal plus oral therapy, current evidence suggests that it is better to start basal insulin early and intensify therapy by adding rapid-acting insulins at mealtimes or switching to a two or three times daily analogue pre-mix regimen rather than using twice-daily basal dosing. ■

With the weight of evidence supporting the early initiation of insulin therapy for improved long-term outcomes, basal plus oral therapy offers a simple, tolerable and acceptable regimen.

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