Management of Type 2 Diabetes – The Role of Basal Insulin

a report by

Vivian Fonseca

Professor of Medicine, Tullis-Tulane Alumni Chair in Diabetes and Chief of the Section of Endocrinology, Tulane University Medical Center

DOI: 10.17925/EE.2007.00.01.37

Type 2 diabetes and its complications are affecting increasing numbers of people worldwide. The burden of serious complications can be considerable for the individual and for the healthcare system. Many of these complications can be prevented or their progression halted with good early management of the condition, including effective management of blood glucose levels. In addition, people with poorly controlled diabetes are at higher risk of cardiovascular disease events, which are a major cause of morbidity and mortality.

Recognising the progressive nature of type 2 diabetes, treatment programmes incorporating the use of insulin earlier in its course are receiving increasing attention.

Large-scale clinical trials have demonstrated the benefits of tight control in type 2 diabetes, minimising disease complications and improving quality of life.[1,2] Recognising the progressive nature of type 2 diabetes, treatment programmes incorporating the use of insulin earlier in its course are receiving increasing attention. The United Kingdom Prospective Diabetes Study (UKPDS) Group followed nearly 3,900 patients with type 2 diabetes receiving intensive therapy with a sulphonylurea or insulin over 10 years and compared these patients with a control group receiving conventional treatment (dietary therapy alone). The patients who received intensive therapy had a 25% risk reduction in microvascular end-points compared with those who received conventional therapy.

During the past several years, developments of several new oral antidiabetic agents and insulin preparations have expanded therapeutic choices for glycaemic control, more effectively enabling patients to reach and maintain blood glucose targets.[3] These developments also allow for a choice of effective combinations of therapeutic agents to meet goals. Insulin remains an important treatment option among these. The purpose of this article is to highlight how insulin can be used effectively in clinical practice in order to get patients to recommended goals.

Insulin – Still a Treatment Option

Type 2 diabetes is characterised by decreased sensitivity of body tissues to insulin. However, even in insulin-resistant subjects, type 2 diabetes develops only when there is a relative deficiency of insulin secretion from the pancreas. This pancreatic defect progresses despite therapy and, over time, most patients have very little residual insulin secretion and require exogenous insulin replacement. In addition, it is recognised that about 10% of people with apparent type 2 diabetes have evidence of autoimmune disease that is associated with earlier loss of beta-cell function than in classic type 2 diabetes.[4] Thus, over time, insulin therapy becomes important for most patients with type 2 diabetes.

Type 2 diabetes is initially treated by lifestyle change, including exercise and diet to induce moderate weight loss, especially in obese patients. Recent guidelines recommend concomitant initiation of pharmacological therapy at the time of diagnosis, usually with oral agents such as metformin.[3] The recommended treatment regimen is focused on the goal of haemoglobin A_{1c} (HbA_{1c}) of <7% with the addition of another agent if the goal is not met or maintained. The UKPDS and A Diabetes Outcome Progression Trial clearly demonstrate that monotherapy with most oral agents is likely to fail within a few years, albeit at different rates.[5,6] Thus, combination therapy is likely to be needed in most cases. The next step in the treatment algorithm offers various choices, including insulin because it is most likely to get patients to goal. However, it is unlikely that most patients and clinicians will move to insulin therapy at this stage. Thus, most patients are

Vivian Fonseca is Professor of Medicine, the Tullis-Tulane Alumni Chair in Diabetes and Chief of the Section of Endocrinology at Tulane University Medical Center in New Orleans, Louisiana. He serves on the clinical practice committee of the American Diabetes Association (ADA), of which he is Chairman, and the joint ADA/American College of Cardiology Make the Link programme. Dr Fonseca has been Editor-in-Chief of *Diabetes Care* since 2007, having formerly been Associate Editor. He was Editor-in-Chief of the *Journal of the Metabolic Syndrome and Related Disorders* until 2006. He served on the editorial board of the *Journal of Clinical Endocrinology and Metabolism* and is an *ad hoc* reviewer for several other journals. Dr Fonseca is a Fellow of the American Association of Clinical Endocrinologists (AACE), the Royal College of Physicians (RCP) and the American College of Physicians (ACP). He is a Member of the Endocrine Society, ADA and the International Diabetes Federation (IDF), serves on several national and international committees and has published more than 200 papers, review articles and book chapters. Dr Fonseca's current research interests include the prevention and treatment of diabetic complications and risk-factor reduction in cardiovascular disease. He has a research programme evaluating homocysteine and inflammation as risk factors for heart disease in diabetes. Dr Fonseca is an investigator in the Action to Control Cardiovascular Risk in Diabetes study, a co-investigator in the National Institutes of Health Targeting Inflammation with Salsalate in Type 2 Diabetes study and serves on the Glycaemia Control Committee and the Steering and Ancillary Studies Committees.

Table 1: Frequently Used Insulin Preparations – Comparison of Human Insulins and Analogues

Preparation	Onset	Peak	Duration
Lispro/Aspart	5–15 minutes	1–2 hours	4–6 hours
Regular	30–60 minutes	2–4 hours	6–10 hours
NPH/Lente	1–2 hours	4–8 hours	10–20 hours
Glargine	1–2 hours	Flat	~24 hours
Detemir	1–2 hours	Less flat	12 hours

The time-course of action of any insulin may vary in different individuals or at different times in the same individual. Because of this variation, time periods indicated here should be considered general guidelines only.

Table 2: Summary of the Two Treatment Titration Regimens for Insulin Glargine Used in Getting Patients to Goal[10]

	Increase in Daily Basal Insulin Glargine Dose (IU)*	
Mean fasting blood glucose for the previous three consecutive days	Algorithm 1: titration at every visit; managed by physician	Algorithm 2: titration every three days; managed by subject
100mg/dl and <120mg/dl (5.5mmol/l and <6.7mmol/l)	0–2 (at the discretion of the investigator)	0–2 (at the discretion of the investigator)
120mg/dl and <140mg/dl (6.7mmol/l and <7.8mmol/l)	2	2
140mg/dl and <180mg/dl (7.8mmol/l and <10mmol/l)	4	2
180mg/dl (10mmol/l)	6–8 (at the discretion of the investigator)	2

** Target FBG 100mg/dl (5.5mmol/l).*
Reviewed by physician at each visit, either in person or over the telephone; titration occurred only in the absence of blood glucose levels <72mg/dl (<4.0mmol/l).
Magnitude of daily basal dose was at the discretion of the investigator.

treated with two or three drug combinations of oral agents such as metformin and sulphonylureas/thiazolidinedione or incretin-based therapy before starting insulin.

If these fail to maintain good control, insulin therapy is the next step, usually as an adjunct to oral medication rather than a complete change in therapy. To minimise the number of injections, insulin therapy is often initiated with a single injection of long-acting insulin. Many studies have demonstrated the advantages of using this single injection at night. This is usually more convenient for patients and also leads to improved fasting blood glucose the next morning, possibly allowing oral agents to work more effectively during the day.

Early use of insulin could theoretically delay the pancreatic dysfunction that culminates in the loss of insulin production, as signalled by the failure of oral agents among patients with long-standing type 2 diabetes.

Should Insulin Be Used Earlier?

Traditionally, practitioners had reserved insulin therapy for patients with type 2 diabetes until diet, exercise and treatment with oral agents failed to maintain glycaemic control. However, there is increasing evidence supporting the earlier use of insulin therapy in the treatment of diabetes, not only to normalise glycaemic control and emulate normal physiological insulin secretion, but also to delay or prevent disease-associated co-morbidity. This concept is being tested in a large multicentre trial.[7]

Early use of insulin could theoretically delay the pancreatic dysfunction that culminates in the loss of insulin production, as signalled by the failure of oral agents among patients with long-standing type 2 diabetes. If insulin therapy is postponed until all oral agents fail, the insulin programme must be more aggressive; single daily injections, alone or in combination with oral agents, are often ineffective.

Starting Insulin Therapy

In recent years the trend in diabetes management has been for a physiological approach to insulin therapy. This usually consists of a basal insulin (a long-acting formulation given once daily) and a pre-prandial insulin, which is ideally both rapid- and short-acting.

The newer insulin analogues have been shown to follow normal insulin-secretory patterns more closely than existing treatments and may therefore provide more effective treatment options.

However, patients may find it daunting to start with three or four injections daily. Therefore, a single injection of a basal insulin – used in conjuction with oral agents – or the twice-daily use of short- and long-acting insulin mixtures, is sometimes used. The pharmacodynamics of some insulin preparations are summarised in *Table 1*.

Before the approval of the basal long-acting insulin analogues (in 2000 for insulin glargine, Lantus; and 2004 for insulin detemir, Levemir), intermediate-acting preparations such as isophane insulin (NPH) were frequently used as basal insulin, and regular insulin was used as the prandial insulin. The approval of the basal long-acting insulin analogues was a major breakthrough in the treatment of diabetes. The newer insulin analogues have been shown to follow normal insulin-secretory patterns more closely than existing treatments and may therefore provide more effective treatment options.

If fasting glucose is elevated, it seems appropriate to target this time of day initially, since lowering fasting glucose towards the normal range could lead to lowering the post-prandial glucose excursions. Thus, the addition of basal insulin, usually given at night to lower the fasting glucose, to patients on oral agents who are not achieving therapeutic targets would be appropriate.

In the Treat-to-Target Trial,[8] the long-acting insulin glargine was compared with NPH. A primary end-point of this study was to reduce HbA_{1c} and the associated hypoglycaemic risk in combination. Both insulins were given at night, starting with 10 units, with an aggressive dose titration to achieve a fasting glucose of less than 100mg/dl. Both of these insulins resulted in a significant decline in fasting glucose and

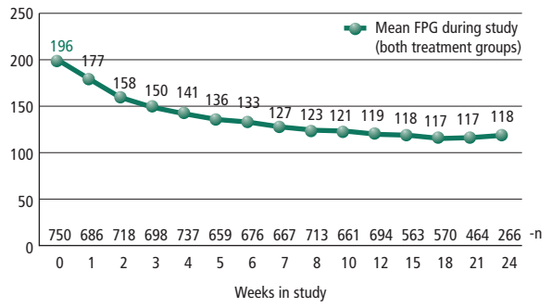
HbA_{1c}, with no difference between groups (see *Figure 1*). Approximately 60% of patients achieved target HbA_{1c} concentrations of less than 7% within the 24-week trial period. However, use of glargine was associated with significantly fewer episodes of hypoglycaemia – including nocturnal hypoglycaemia – compared with NPH, thus achieving the primary end-point of not only reducing HbA_{1c}, but also doing so with significantly less hypoglycaemic risk. Similar results have been obtained with detemir insulin when added as basal insulin to patients with type 2 diabetes suboptimally controlled on oral agents.[9]

When starting basal insulin, it makes sense to continue the oral agents at the same dose initially, at least until a prandial insulin is added. A single, small, evening dose of glargine or detemir at bedtime is advisable, and the dose adjusted according to the fasting-glucose concentration. The Treat-to-Target algorithm has been successfully applied to clinical practice to get patients to goal.[10,11] It is possible to teach patients to make their own adjustments in insulin dose based on their own fasting glucose.

Next Steps

If a patient is still not achieving the goal for HbA_{1c} despite adequate titration of bedtime basal insulin, it usually indicates post-prandial hyperglycaemia or lack of compliance. The former can be addressed by moving the patient to the next step of therapy – basal bolus treatment with pre-prandial injections of rapid-acting analogues. Usually, it is appropriate to discontinue sulphonylureas at this stage, but continue with sensitisers. Even this step can be gradually introduced, with the short-acting insulin initially given only with the main meal of the day and then gradually increased in frequency and dose. With such a strategy it is possible to get most patients to the stated goals and decrease their risk of long-term complications of diabetes. ■

Figure 1: Fasting Blood Glucose Results in the Treat-to-Target Trial with both Insulin Glargine and NPH



1. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34), UK Prospective Diabetes Study (UKPDS) Group, *Lancet*, 1998;352:854–65.
2. Nathan DM, Cleary PA, Backlund JY, et al., Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes, *N Engl J Med*, 2005;353:2643–53.
3. Nathan DM, Buse JB, Davidson MB, et al., Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes, *Diabetes Care*, 2006;29:1963–72.
4. Palmer JP, Hampe CS, Chiu H, et al., Is latent autoimmune diabetes in adults distinct from type 1 diabetes or just type 1 diabetes at an older age?, *Diabetes.* 2005;54 Suppl 2:S62–7.
5. Turner RC, Cull CA, Frighi V, Holman RR, Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49), UK Prospective Diabetes Study (UKPDS) Group, *JAMA*, 1999;281:2005–12.
6. Kahn SE, Haffner SM, Heise MA, Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy, *N Engl J Med*, 2006;355:2427–43.
7. http://clinicaltrials.gov/ct/gui/show/NCT00069784
8. Riddle MC, Rosenstock J, Gerich J, The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients, *Diabetes Care*, 2003;26:3080–6.
9. Meneghini LF, Rosenberg KH, Koenen C, et al., Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study, *Diabetes Obes Metab*, 2007;9:418–27.
11. Davies M, Storms F, Shutler S, et al., Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine, *Diabetes Care*, 2005;28:1282–8.
12. Rosenstock J, Basal insulin supplementation in type 2 diabetes; refining the tactics, *Am J Med*, 2004;116(Suppl.3A):10S–16S.

A Selection of Recent Articles of Interest Co-authored by Vivian Fonseca

Differential Effect of Beta-blocker Therapy on Insulin Resistance as a Function of Insulin Sensitizer Use: Results from GEMINI
Diabet Med
2007;19 [Epub ahead of print]
Fonseca V, Bakris GL, Bell DS, McGill JB, Raskin P, Messerli FH, Phillips RA, Katholi RE, Wright JT Jr, Waterhouse B, Lukas MA, Anderson KM; for the GEMINI Investigators.

Beta-blocker Use and Diabetes Symptom Score: Results from the GEMINI Study
Diabetes Obes Metab
2007;9(3):408–17.
McGill JB, Bakris GL, Fonseca V, Raskin P, Messerli FH, Phillips RA, Katholi RE, Wright JT Jr, Iyengar M, Anderson KM, Lukas MA, Dalal MR, Bell DS.

Addition of Vildagliptin to Insulin Improves Glycaemic Control in Type 2 Diabetes
Diabetologia
2007;50(6):1148–55. Epub 2007 Mar 27
Fonseca V, Schweizer A, Albrecht D, Baron MA, Chang I, Dejager S.

Primary Prevention of Cardiovascular Diseases in People with Diabetes Mellitus: a Scientific Statement from the American Heart Association and the American Diabetes Association.
Diabetes Care
2007;30(1):162–72. Review.
Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW, Pignone MP, Plutzky J, Porte D, Redberg R, Stitzel KF, Stone NJ; American Heart Association; American Diabetes Association.

Primary Prevention of Cardiovascular Diseases in People with Diabetes Mellitus: a Scientific Statement from the American Heart Association and the American Diabetes Association
Circulation
2007;Jan 2;115(1):114–26. Epub 2006 Dec 27.
Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW, Pignone MP, Plutzky J, Porte D, Redberg R, Stitzel KF, Stone NJ; American Heart Association; American Diabetes Association.

The Effectiveness of Intensive Glycemic Control for the Prevention of Vascular Complications in Diabetes Mellitus
Treat Endocrinol
2006;5(5):273–86.
Vasudevan AR, Burns A, Fonseca VA.