Initiation of Insulin Treatment in Type 2 Diabetes Mellitus

a report by
Geremia B Bolli

Professor of Medicine, Department of Internal Medicine, Section of Internal Medicine, Endocrinology and Metabolism, University of Perugia

DOI: 10.17925/EE.2007.00.01.40

Type 2 diabetes mellitus (T2DM) is a frequently occurring disease and its incidence and prevalence is expected to increase considerably all over the world. T2DM is an important disease because of the frequent complications (micro- and macrovascular) that may occur after several years, resulting in reduced life expectancy, as well as miserable quality of life and an increasing economic burden.

However, prevention of high blood glucose (BG) and maintenance of glycated haemoglobin A1C <7.0% have been demonstrated to reduce the incidence of all complications of T2DM. Therefore, it is essential that T2DM is not only prevented (i.e. by tackling obesity and implementing an active lifestyle), but is also diagnosed early and treated aggressively from its initial phase to prevent the onset of complications.

Unfortunately, risk factors for T2DM such as obesity are often not treated. In addition, T2DM itself is often undiagnosed and, when diagnosed, remains – in the majority of cases – undertreated with fasting and post-prandial BG, as well as A1C, all above the recommended targets. No surprise, then, that under these conditions T2DM continues to be a major problem for affected patients.

Among other reasons (poor diet and lack of physical exercise), one factor of poor BG control in T2DM is the late use of insulin. Doctors claim that it is the T2DM patients who do not accept insulin treatment, but in reality it is the doctors who do not have the culture of 'early insulinisation' and its commensurate benefits and advantages to improve prognosis of the disease. The modern concept of early insulinisation with once-daily administration of basal insulin may improve compliance of doctors and patients and play a major role in reducing A1C in the T2DM population.

Initial Treatment of the Disease

The modern goals of treatment of T2DM are maintaining A1C <7.0% and preventing hypoglycaemia, as well as increasing awareness of the disease. In addition to education and motivation of diabetic subjects to maintain an appropriate lifestyle (diet, physical exercise), oral drugs and/or insulin should be started from diagnosis, the exception being those individuals who can control hyperglycaemia very quickly (in a few days) with high adherence to diet and exercise. In the majority of subjects, metformin should be given (0.5g/6h) alone, or in combination with a secretagogue. Long-acting sulphonylureas (SUs) can be used once daily, but the rapid-acting secretagogues glinides (nateglinide, repaglinide) should be preferred to SU at mealtime because of the lower risk of hypoglycaemia. In the near future, oral inhibitors of dipeptidyl peptidase-4 (DPP-4) at mealtime (or injectable glucagon-like peptide-1 (GLP-1) analogues) may replace glinides, but their accessibility will be limited by the high cost. The role of thiazolidinedions (TZDs) is uncertain at the moment. These drugs are not life-saving, they increase body weight (although the claim is 'good obesity' due to fat redistribution from visceral to subcutaneous compartment) and in a small percentage of subjects may induce bone fractures. Above all, the long-term effects of TZDs are not known.

The modern concept of early insulinisation with once-daily administration of basal insulin may improve compliance of doctors and patients and play a major role in reducing A1C in the type 2 diabetes mellitus population.

Postponing Insulin

Many studies indicate that it is possible to decrease elevated A1C (8.0%, 9.0% or greater) by adding a third or fourth oral drug. For example, when metformin+SU fails, addition of either a TZD or DPP-IV inhibitor may reduce A1C by 0.5–1.0%.

This is the wrong approach. First of all, the patients in question generally have long-term T2DM with advanced pancreatic islet failure. They need insulin substitution. Of course, adding new drugs may temporarily improve the A1C, but it is of note that A1C never comes back consistently to <7.0% and remains there. In addition, the studies are of short duration (usually six months) and it is expected that long-term observation would reveal loss of control again shortly after.

Basal Insulin

Until A1C remains <7.0%, T2DM patients can continue the above treatment. However, as soon as A1C increases consistently >7.0%, additional measures should be taken. The most efficient step is to start

Geremia B Bolli is Professor of Medicine in the Department of Internal Medicine, Section of Internal Medicine, Endocrinology and Metabolism, at the University of Perugia. His primary research interests include the physiology of glucose counter-regulation to hypoglycaemia, the pathophysiology of hypoglycaemia and the long-term optimisation of glycaemic control in type 1 and type 2 diabetes. Professor Bolli has been an Associate and Deputy Editor-in-Chief of *Diabetologia* and is a member of the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA). Professor Bolli graduated from the Perugia University School of Medicine in 1972.

basal insulin (neutral protamine hagedorn (NPH), or glargine or detemir) once daily. The modern concept is early insulinisation, which means starting insulin before marked loss of BG control takes place. The rationale of early insulinisation is two-fold: not only to efficiently improve the control of BG (insulin is the easiest way of controlling BG), but also to modify the natural history of decline of beta-cell function over time. This can be achieved by better preserving, for longer, the pancreatic islet (not only beta-, but also alpha-cell) function. Studies *in vitro* and initial evidence *in vivo* strongly argue in favour of insulin versus SU as a good agent to preserve beta-cell function. With this in mind, it is never too early to start insulin. In fact, treatment with insulin at the diagnosis of T2DM is recommended to take immediate control of BG on one hand but, on the other, also to demonstrate to the patient how easy, efficient and simple insulin treatment is. This initial insulin treatment can be withdrawn later as soon as the patient improves in terms of BG control and oral agents can be started. Later, if the patient needs insulin, it is likely he or she will have good memories of previous insulin experience and will be not frightened by the idea of starting insulin treatment.

Treatment with insulin at the diagnosis of type 2 diabetes mellitus is recommended to take immediate control of blood glucose on one hand, but, on the other, also to demonstrate to the patient how easy, efficient and simple insulin treatment is.

With basal insulin, oral agents should be continued (secretagogues will eventually be reduced to prevent hypoglycaemia). Basal insulin should be titrated to normalise BG, a pre-requisite to lowering A1C <7.0%. In theory, such a result may be achieved with any basal insulin, but it is easier with the nearly peakless glargine than with the peak NPH because of lower risk of nocturnal hypoglycaemia. This is especially true when titration becomes aggressive to 'normalise' fasting BG. Also, insulin detemir is better than NPH in preventing nocturnal hypoglycaemia, but because of its shorter duration of action versus glargine in a substantial number of T2DM subjects insulin detemir has to be given twice daily.

If the old, inexpensive NPH insulin is started, the time of injection should be at bedtime (23:00–24:00h). NPH is limited in its use by its peak of action, and the rationale of bedtime administration is to reduce the risk for early-night hypoglycaemia. However, as stated, aggressive titration with a peak insulin induces *per se* risk of nocturnal hypoglycaemia and therefore limits the possibility of maintaining the target fasting BG and long-term A1C.

With insulin glargine, the time of administration is less rigid because of its nearly peakless mode of action spread over a 24-hour period. However, it is more convenient to inject glargine at dinnertime because it is easier to titrate the dose against the fasting BG 12 hours later at 7 or 8am, when glargine is most active.

Detemir can be given either at dinner or bedtime, but the former is perhaps preferable in view of the possible need for a second administration 12 hours later.

The dose of basal insulin should be started as 10U, and increased by 2–4U every three days if fasting BG remains >100mg/dl. Larger doses may be initiated in patients with marked hyperglycaemia and insulin resistance.

With basal insulin plus oral agents, about 50% of T2DM subjects reach the target of A1C <7.0%. These patients can continue the convenient treatment of once-daily basal insulin until A1C remains <7.0%. However, for those patients who cannot reach A1C <7.0% or who lose control over time as demonstrated by progressive increase in A1C >7.0%, prandial insulin treatment is recommended in addition to basal insulin.

Prandial Insulin

A rapid-acting analogue (lispro, aspart or glulisine) or inhaled insulin should be given at mealtime, or any time patients take a carbohydrate-rich meal. At this stage, which reflects a late stage of T2DM with advanced deterioration of pancreatic insulin release, the insulin regimen consists always of basal insulin replacement and prandial replacement.

The basal-insulin supplementation becomes more challenging in people with long-standing T2DM and advanced beta-cell failure. Risk of hypoglycaemia is greater. This is certainly the case when NPH becomes more limiting in its use because of greater risk of nocturnal hypoglycaemia. In this situation particularly, long-acting insulin analogues should be preferred to NPH, with the above specifications relative to differences between glargine and detemir.

The prandial insulin should be used with caution in relation to carbohydrates ingested. This is the time where patients need to learn about BG monitoring before and 2h after meals to decide the prandial insulin dose based on what they are going to eat in terms of carbohydrates.

Why Pre-mixed Insulins Should Not Be Used

Pre-mixed insulins (usually 30% rapid-acting, 70% NPH) should not be used because of high risk of hypoglycaemia before lunch and after midnight, especially when the goal is A1C <7.0%. Instead of being a simple treatment, they complicate life for patients by introducing fluctuations of BG until low values result. This risk increases in people with long-term T2DM who have fragile defences against hypoglycaemia because of impaired counter-regulation (reduced release of glucagons secondary to beta-cell failure).

Conclusion

Insulin is not a drug. It is a natural hormone that is missing in people who have T2DM. Although the consensus is that treatment of insulin resistance (diet, exercise, metformin) is the key approach to keep A1C <7.0% in T2DM, insulin should be considered as the ideal partner of treatment at an early stage of T2DM. In many patients only basal insulin – a simple and well-accepted treatment – is needed, perhaps because T2DM is still at an early stage. Early insulin treatment may preserve pancreatic islet function for a long time, thus preventing the need of full insulin substitution (prandial on top of basal). ■