The case for insulin treatment early in type 2 diabetes

**ABSTRACT**

Most patients with type 2 diabetes ultimately need insulin therapy. This paper presents the case for starting insulin therapy sooner rather than later, preferably without oral drugs and in a “basal/bolus” regimen consisting of a daily dose of a long-acting insulin for basal coverage plus preprandial doses of a short-acting insulin.

**KEY POINTS**

Beta-cell function tends to decline over time in patients with type 2 diabetes as insulin resistance leads to beta-cell exhaustion and elevated lipids and glucose exert toxic effects on beta cells.

Tight control of blood glucose levels is key to preventing the microvascular and possibly the macrovascular complications of diabetes, and is more effectively accomplished with insulin than with oral drugs.

Early insulin therapy with resultant tighter glucose control appears to spare or delay beta-cell damage and might even restore beta-cell function. The beneficial effects of insulin have been shown in randomized controlled trials.

New insulin analogues have more favorable pharmacokinetic profiles than standard insulin preparations, making them more attractive for use in basal/bolus regimens.

**TIGHT CONTROL REDUCES RISK**

Type 2 diabetes causes considerable morbidity and mortality, partly owing to its microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (myocardial infarction, stroke, peripheral vascular disease).

The United Kingdom Prospective Diabetes Study (UKPDS) was the largest and...
The longest-running prospective trial in patients with type 2 diabetes. Patients were randomly assigned to undergo either intensive or conventional treatment; within each treatment group, patients were further randomized to receive either insulin or oral drugs.

Intensive glycemic control significantly reduced the risk of microvascular complications compared with conventional therapy. The relationship between the risk of microvascular complications and glycemia was continuous: for every percentage-point decrease in hemoglobin A1c, the microvascular risk declined by 35%.

The Multiple Risk Factor Intervention Trial (MRFIT) and the Helsinki Heart Study found a strong correlation between type 2 diabetes and macrovascular complications. However, the UKPDS found only a non-significant trend toward reduced cardiovascular risk with intensive vs traditional therapy.

The Verona Diabetes Study identified long-term variability in fasting plasma glucose as an independent predictor of total, cardiovascular, and cancer mortality in patients with type 2 diabetes. Indeed, the coefficient of variation of fasting plasma glucose had greater prognostic value than the mean fasting plasma glucose level itself, which led the investigators to suggest that such variability may have masked the benefits of stringent glucose control in preventing myocardial infarctions in the UKPDS.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) and other studies designed to evaluate the effects of intensive glycemic control on cardiovascular morbidity and mortality are under way.

**GOALS OF TREATMENT**

In view of these data, the American Diabetes Association recommends the following goals:
- Fasting plasma glucose 80 to 120 mg/dL
- Hemoglobin A1c less than 7%

Similarly, the American Association of Clinical Endocrinologists recommends the following goals:
- Fasting plasma glucose lower than 110 mg/dL
- Hemoglobin A1c less than 6.5%
- 2-hour postprandial glucose lower than 140 mg/dL.

Few patients achieve diabetes goals

Even in clinical trials, however, only a minority of patients achieve these goal levels, and despite extensive efforts and more oral drugs available, attempts at reaching and maintaining near-normal glycemic levels in actual clinical practice have been largely unsuccessful.

For example, Hayward et al found that, of 8,668 patients with type 2 diabetes treated by generalist physicians, 60% had hemoglobin A1c values of 8% or higher. Greenfield et al in an analysis of 1,750 patients from 29 sites throughout the United States, estimated the number to be as high as 68%.

**NATURAL HISTORY OF TYPE 2 DIABETES**

In type 2 diabetes, glycemic control gradually but steadily deteriorates over time. Patients who start on oral drugs need to keep escalating the dose and adding more agents. Eventually, most patients require insulin therapy.

For example, in the UKPDS, the median hemoglobin A1c value gradually increased regardless of treatment intensity (FIGURE 1). For the patients receiving insulin monotherapy in this study, a reason for the failure to maintain
glycemic control may have been that the participating physicians were reluctant to aggressively treat to target levels by increasing the insulin dose.

Also in the UKPDS, fewer and fewer patients could maintain glycemic control over time while receiving monotherapy (a sulfonylurea, insulin, or metformin): 47% to 50% at 3 years, 34% to 37% at 6 years, and 24% to 28% at 9 years.

**WHY DOES DIABETES PROGRESS?**

The primary defects in type 2 diabetes are insulin resistance and decreased insulin secretion, though their relative roles in the etiology of the disease remain controversial.

Various degrees of insulin resistance are commonly seen in the general population. This insulin resistance may be mediated in whole or in part by lipolysis and elevated free fatty acid levels.

Insulin resistance alone does not usually give rise to hyperglycemia, because the pancreas can compensate by secreting more insulin. Over time, however, the beta cells may become "exhausted" and produce less insulin. When insulin levels are no longer sufficient to compensate for insulin resistance, hyperglycemia and overt diabetes ensue (FIGURE 2).

Lipolysis and elevated free fatty acid levels may also contribute to beta-cell dysfunction and can chronically elevate blood glucose levels. In vitro, isolated beta cells and human islets that are exposed to high levels of glucose secrete less insulin in response to glucose stimulation. In animal models, sustained hyperglycemia reduces beta-cell mass and impairs beta-cell response to an acute glucose stimulus.

Together, these adverse effects contribute to failure and ultimate loss of beta-cell function in a self-perpetuating cycle of worsening defects and exacerbation of the hyperglycemia. Regardless of mechanism or mechanisms, the bottom line is that beta-cell function deteriorates over time and is ultimately lost.

**Loss begins early**

Data from the UKPDS show the decrease in beta-cell function over time (FIGURE 3). If we extrapolate backward, function appears to begin decreasing about a decade before diagnosis; extrapolating forward, it would be expected to fall to an extremely low level 12 to 15 years after diagnosis.

**ORAL DRUG TREATMENT**

Oral agents have been the mainstays of treatment for type 2 diabetes. They lower hemoglobin A1c through different mechanisms of action (TABLE 1).

**Insulin secretagogues.** The sulfonylureas increase insulin secretion throughout the day; the meglitindes (repaglinide and nateglinide) are shorter-acting and can be taken before meals to increase prandial insulin secretion.

**Insulin sensitizers.** The biguanide metformin and the glitazones enhance insulin action by reducing hepatic glucose output and increasing insulin-dependent glucose disposal.

**Alpha glucosidase inhibitors** reversibly inhibit carbohydrate breakdown in the gut and thus reduce absorption of glucose.
Oral monotherapy ultimately fails

Traditionally, these agents are started as monotherapy, selected on the basis of patient characteristics, plasma glucose levels (fasting and postprandial), and adverse effects of the medication.

A single agent, however, usually fails to control glucose levels over time, even after an initially positive response. After 3 years of monotherapy with insulin, a sulfonylurea, or metformin, approximately 50% of patients in the UKPDS required combination therapy; by 9 years, this percentage had increased to 75%.13

Furthermore, the progressive decline in beta-cell function, as reported in the UKPDS, translates into deterioration of glycemic control and disease progression.28 Thiazolidinediones may preserve beta-cell function, but for how long is not known.24,29

When the decline in beta-cell function cannot be compensated for by increasing the dose of the single agent the patient is receiving, he or she requires combination therapy. By combining oral agents with different mechanisms of action, glycemic control can be achieved and improved. Short-acting insulin secretagogues (nateglinide, repaglinide) can be used before meals for prandial glycemic control, while insulin sensitizers (metformin and the glitazones) can be used to control insulin resistance and between-meal glycemia to provide basal glucose control.

Single-tablet, fixed combinations (rosiglitazone-metformin; metformin-sulfonylurea) are convenient to take but cost more than individual agents, and the individual doses cannot be adjusted.

However, even combination oral therapy eventually fails to maintain glycemic control in most patients.30 Data are scant on triple oral therapy; the single clinical trial performed so far31 showed no restoration of glycemic control when troglitazone (no longer available) was added to a combination of sulfonylurea and metformin. To date, no oral agent or combination has been able to prevent indefinitely the progressive deterioration of glycemic control in type 2 diabetes.3,22–27,29,31,32

**ADDING INSULIN THERAPY**

When glycemic control continues to fail with oral therapy, insulin therapy becomes necessary.

**Usual practice:**

**Add a basal insulin at bedtime**

The usual practice has been to add a bedtime dose of an intermediate-acting insulin such as neutral protamine Hagedorn (NPH) or Lente, or a long-acting insulin such as Ultralente or, more recently, insulin glargine (Lantus), while maintaining the oral agent or agents. A recent trial33 suggests that insulin glargine is more effective than NPH.

A common starting dose is 10 units of NPH, Lente, Ultralente, or insulin glargine, adjusted according to the morning, before-breakfast capillary glucose level. The goal is a before-breakfast capillary glucose level between 80 and 120 mg/dL, although we tend to accept higher levels if the patient is elderly or has comorbidities.

Usually one oral agent is retained. If I follow this approach at all, I prefer a daytime insulin-sensitizing agent such as metformin.
twice daily, if tolerated, with bedtime insulin glargine. However, a daytime oral agent with bedtime insulin may not provide long-term satisfactory glycemic control. A full insulin program (insulin monotherapy) is then required, and oral agents should be completely discontinued.

### WHY NOT START INSULIN SOONER?

Starting insulin therapy earlier in treatment provides tighter glucose control than oral treatment, and may therefore relieve and spare beta-cell function, help lower insulin resistance, and reduce lipotoxicity and glucose toxicity.31

### The author’s approach

I prefer to start insulin initially if the patient’s plasma glucose level is greater than 200 mg/dL, and continue it indefinitely unless “remission” occurs, requiring stopping insulin until significant hyperglycemia (> 140 mg/dL) recurs.

If the patient prefers oral agents initially, I
try short-term insulin therapy for glucose levels greater than 200 mg/dL and then make the transition to oral agents. However, once they try it, most patients stay on insulin. If beta-cell function is restored, the patient can continue hygienic measures until significant hyperglycemia recurs.

For patients with glucose levels lower than 200 mg/dL at diagnosis, I try diet, exercise, and selective oral agents (secretagogues or metformin, rarely thiazolidinediones) but switch to insulin if glycemic control is not satisfactory.

### Benefits of insulin therapy

In various studies, temporary, short-term intensive insulin therapy in both lean and obese patients with severe type 2 diabetes produced optimal glycemic control by enhancing insulin action, decreasing hepatic glucose production, and improving beta-cell function. These benefits were maintained for at least 1 week after insulin therapy was discontinued.

Short-term insulin treatment may have long-lasting effects when introduced in the early stages of type 2 diabetes. Ilkova et al36 found that newly diagnosed, mildly overweight patients with hyperglycemia achieved near-normoglycemia within days of beginning treatment with moderate doses of insulin. Treatment lasted for 2 weeks; adequate glycemic control persisted for at least 6 months after treatment stopped in 85% of the patients, all of whom were controlled on diet alone.36

Similarly, in nonobese patients with newly diagnosed type 2 diabetes, early insulin therapy induced optimal glycemic control that persisted without oral or insulin therapy after the study ended.37

Insulin therapy early in the treatment of type 2 diabetes may reverse some effects of glucose toxicity and lipotoxicity, improving both insulin sensitivity and insulin secretion and reestablishing optimal control.22 These metabolic improvements may spare beta cells and break the cycle of dysfunction, hyperglycemia, and worsened dysfunction that maintains the diabetic state.

Starting insulin therapy early in treatment rather than as the last option might delay the progression of type 2 diabetes and possibly prevent the development or delay the progression of the associated microvascular and macrovascular complications (as suggested from the UKPDS data).

If a patient with type 2 diabetes achieves restoration of beta-cell function (previously termed “clinical remission”), he or she should be maintained on treatment with diet, weight control, and exercise. In my experience, this happens in about 10% of cases. My criteria for trying to stop insulin are two blood sugar measurements at target levels, hemoglobin A1c at target level, or hypoglycemia.

When hyperglycemia intervenes again, I believe that patients should resume insulin monotherapy rather than try oral agents. However, if oral agents are tried, their effectiveness should be closely monitored and insulin monotherapy promptly resumed if they fail, as measured by two consecutive hemoglobin A1c measurements greater than 6.5% or two plasma glucose measurements greater than 140 mg/dL, or both.

Long-term studies are needed to address further the beneficial effects of early insulin therapy in type 2 diabetes mellitus on beta-cell function, microvascular and macrovascular morbidity and mortality, and total mortality.

### INSULIN OPTIONS

The goal of insulin therapy is to mimic normal endogenous insulin secretion to provide near-physiologic control of glycemic levels.

Insulin formulations are classified according to their onset and duration of action (Table 2).38–40

#### Short-acting insulins

Short-acting insulins are taken before meals to replace the missing endogenous secretion that normally would take place in response to a meal.

Regular insulin has a relatively long time to peak effect and a long duration of action, necessitating that the patient follow a rigid schedule, giving oneself the injection and then waiting about a half an hour before eating to match the onset of action and peak action of regular insulin with the postprandial glycemic peak.
Insulin therapy may reverse some of the effects of glucose toxicity

Insulin lispro, an insulin analogue available since the mid 1990s, and the newer analogue insulin aspart have faster onsets and shorter durations of action than regular insulin, making them more convenient to take before meals.41–43

**Intermediate-acting insulins**

NPH and Lente are intermediate-acting insulins used to replace normal basal insulin secretion (between meals and overnight).

However, the pharmacokinetic characteristics of these preparations (TABLE 2) do not closely approximate those of normal basal insulin secretion. For example, they reach a peak of action a few hours after subcutaneous injection, during which the insulin level may be too high, increasing the risk of hypoglycemia, particularly at night.44–46 Moreover, their durations of action do not cover the 24-hour, daylong basal insulin needs.

**Long-acting insulins**

Long-acting Ultralente also exhibits a peak action profile and may therefore also produce overinsulinization and increase the risk of hypoglycemia.47,48

Insulin glargin, a basal insulin analogue, has characteristics that mimic physiologic basal insulin secretion: a smooth, constant time/concentration profile that lasts approximately 24 hours with no pronounced peak. It also has less variability in its absorption than other intermediate-acting and long-acting insulins.39,49

Insulin detemir, a new human insulin derivative with 24-hour peakless activity, is being evaluated for use as a basal insulin. It has the potential advantage of being able to be mixed in the same syringe with short-acting insulins, unlike insulin glargin.50

**Optimum insulin regimens**

The current optimum insulin regimens that closely mimic beta-cell function are:

- Basal/bolus therapy: morning or bedtime insulin glargin (basal component) combined with mealtime insulin lispro or insulin aspart (bolus component for mealtime glucose control). TABLE 3 outlines the steps in initiating insulin monotherapy.
- Insulin pump therapy with insulin lispro or insulin aspart.

Premixed insulins with fixed proportions of intermediate-acting and short-acting insulins such as 70/30, 70/25, and 50/50 are less desirable in initial diabetes management because one cannot titrate the proportions more precisely for optimum glycemic control. However, these preparations have a role in some patients who are elderly or who have comorbidities and difficulties with mixing insulins.

### OVERCOMING BARRIERS TO INSULIN THERAPY

Barriers to the early use of insulin therapy for type 2 diabetes include physician concerns about causing cardiovascular disease, weight gain, and hypoglycemia; patient nonacceptance of insulin therapy; and lack of time in the physician’s schedule to manage insulin therapy.

Does insulin therapy cause cardiovascular disease?

Several epidemiologic studies51–53 found a correlation between endogenous hyperinsulinemia and risk of coronary heart disease. These findings caused considerable apprehension about exogenous insulin therapy because of the fear of exposing patients to potentially deleterious hyperinsulinization.
Data from the 1990s, however, show no evidence to link insulin therapy and atherogenesis.

The University Group Diabetes Program found no association between insulin therapy and adverse cardiovascular outcomes. In fact, a trend toward improvement of cardiovascular end points was seen instead. The UKPDS found no increase in myocardial infarctions among patients assigned to insulin therapy, and macrovascular surrogate end points did not differ from those observed in the conventional treatment groups. These patients had higher fasting insulin levels, but this had no adverse effect on macrovascular complications.

The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study found that patients with type 2 diabetes who received a glucose-insulin infusion during an acute myocardial infarction followed by intensive insulin therapy had a 30% lower mortality risk after 1 year compared with those receiving standard therapy.

Moss et al and Hellman et al in observational studies, also found lower rates of cardiovascular and total mortality among patients receiving intensive insulin therapy.

Benefits of tight control offset the impact of weight gain

Modest weight gain is a recognized side effect of insulin therapy. In the UKPDS, patients in the intensive insulin treatment group gained significantly more weight than those in the conventional treatment group (P < .001). Nevertheless, the benefits of stringent glycemic control clearly offset the impact of weight gain.

The use of metformin with insulin helps limit weight gain and reduces exogenous insulin requirements. However, I do not continue the metformin with full insulin monotherapy.

Hypoglycemia tends to be mild or moderate

The UKPDS showed that intensive insulin therapy does carry a greater risk of inducing hypoglycemia than do sulfonylurea or metformin in type 2 diabetic patients. Most hypoglycemic events with insulin therapy were mild to moderate, however, and severe episodes were significantly less frequent than commonly observed in patients with type 1 diabetes.

Short-acting and long-acting peakless insulin analogues are associated with a lower incidence of hypoglycemia than are traditional insulin preparations.
EARLY INSULIN IN TYPE 2 DIABETES

PALUMBO

Education leads to acceptance

Physicians can address the barriers of patient nonacceptance of insulin therapy and of the perception of worsening disease by explaining how insulin production decreases over time, the reason for all the injections and finger-sticks, the goals of therapy, and how insulin therapy will assure that these goals are achieved and thereby reduce the risk of complications and death.

Physician efficiency in initiating and maintaining insulin therapy can be improved by use of a registered dietitian or certified diabetes nurse educator as part of the health care team.

Generally, both physicians and patients see insulin therapy as the last resort in managing type 2 diabetes. Influenced by the limitations imposed by most health care settings (eg, constraints in doctor visit duration), physicians perceive the management of insulin treatment as overwhelming and are therefore reluctant to prescribe it. The patient’s fear of the invasiveness of insulin injections and increased frequency of glucose self-monitoring are additional major barriers to insulin implementation.

Insulin delivery tools such as pen-type injection systems are convenient, and one can try different regimens and insulin formulations that allow for fewer injections. However, maintaining adequate glycemic control is paramount. Less-invasive devices for glucose monitoring are also available.

Perhaps the most important point to emphasize to both physicians and patients is that early use of insulin therapy, either when type 2 diabetes is first diagnosed or promptly when oral therapy fails, will reduce deterioration of metabolic control, which translates into improved overall health, improved quality of life with decreased comorbidities, and a longer life expectancy.

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