Addition of Insulin to Oral Therapy in Patients with Type 2 Diabetes

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ABSTRACT: *Background:* A majority of individuals with type 2 diabetes will eventually require exogenous insulin therapy to achieve or maintain glycemic control. This review provides practical recommendations for adding insulin therapy for patients with type 2 diabetes whose glucose levels are inadequately controlled with oral medications. *Methods:* We used a systematic review of MEDLINE to retrieve relevant articles from 1990 to 2004 using the search terms *insulin therapy, combination oral therapy, glycemic control, insulin analogs, insulin glargine,* and *basal insulin,* which we supplemented with a review of clinical practice guidelines from the American Diabetes Association and the American Association of Clinical Endocrinologists. *Results:* Type 2 diabetes mellitus is becoming more common in the United States and is likely to increase in prevalence as obesity, a risk factor for type 2 diabetes, likewise increases. Treatment often begins with oral monotherapy, but after 3 years of treatment, more than half of patients will require more than one pharmacological agent, and eventually most patients will require insulin. Adding insulin to oral therapy at an earlier stage in treatment provides improved glycemic control without promoting increased hypoglycemia or weight gain, lowers the risk of microvascular complications by 25%, and reduces the amount of insulin patients require. Various insulin preparations, including the newer analog insulins, with different onsets and durations of action are available to help meet individual patients' dosing needs. *Conclusions*: The addition of insulin to oral antidiabetic therapy can improve glycemic control. Newer insulin analogs can emulate normal physiologic insulin secretion and potentially limit diabetes-related comorbidity. **KEY INDEXING TERMS:** Diabetes; Insulin; Oral diabetic agents; Glycemic control; Hypoglycemia. **[Am J Med Sci 2006;331(5):257–263.]**

Case Report

An obese 48-year-old white woman with diabetes presents for a follow-up visit. She had gestational diabetes and weight gain with the births of her three children and has a family history of diabetes, dyslipidemia, and coronary artery disease. During pregnancy, her diabetes was diet-controlled. After her last pregnancy, when she was 39 years old, she was told her cholesterol level was "a little high." She was referred to a nutritionist and advised to begin an exercise program. At the age of 44 years, she was diagnosed with type 2 diabetes. She is currently taking metformin and a sulfonylurea. On a previous visit, the patient's glycosylated hemoglobin (A1C) concentration was 6.5%. The latest test result shows an increase to 7.2%.

This case is representative of many individuals with type 2 diabetes in which disease progresses despite oral medication. What is the optimal treatment for patients with rising A1C concentrations who are already receiving combination oral antidiabetic therapy? This article provides practical recommendations for adding insulin therapy in patients with type 2 diabetes whose glucose levels are inadequately controlled with oral medications.

Treatment Goals in Type 2 Diabetes

One of the primary goals of treatment in patients with type 2 diabetes is to lower plasma glucose levels to prevent the microvascular and macrovascular complications associated with chronic hyperglycemia.[1–4] The American Diabetes Association (ADA) and the American College of Endocrinology (ACE) have developed guidelines for glycemic control (Table 1).[5] The ACE has set stricter standards for glycemic control than the ADA, citing substantial evidence supporting the benefits of better-controlled plasma glucose levels.[4] Data from the National Health and Nutrition Examination Survey III show that despite antidiabetic therapy, more than half of

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Table 1. American Diabetes Association (ADA)[2] and American College of Endocrinology (ACE)[4] Recommendations for Glycemic Control in Adults With Diabetes Mellitus

Parameter	ADA Target Value	ACE Target Value
A1C	<7.0%[a]	≤6.5%[b]
Preprandial plasma glucose	90–130 mg/dL (5.0–7.2 mmol/L)	<110 mg/dL
Peak postprandial plasma glucose	<180 mg/dL (<10.0 mmol/L)	NA
2-Hour postprandial blood glucose	NA	<140 mg/dL

[a]*Compared with nondiabetic range of 4.0% to 6.0% based on a Diabetes Control and Complications Trial–based assay.*
[b]*Assess twice a year for patients with values at target; assess quarterly or more frequently for patients with values above target and patients in whom treatment is altered.*

patients in the United States with type 2 diabetes have not attained the ADA's glycemic control goal of A1C less than 7.0%.[5]

Limitations of Current Treatment

Treatment of patients with type 2 diabetes often begins with monotherapy using an oral hypoglycemic agent from one of five classes: sulfonylureas, meglitinides, thiazolidinediones, biguanides, and α-glucosidase inhibitors.[6] If glycemic control worsens, a second oral agent is usually added.[6] Studies show that after 3 years of treatment, approximately 50% of patients require more than one pharmacological agent,[7] and most patients with type 2 diabetes eventually require insulin.[8] Currently, 6 to 7 million Americans with diabetes (types 1 and 2) use human insulin or insulin analogs (types 1 and 2)[8]; approximately 30% of patients with type 2 diabetes receive insulin therapy.[9]

Failure to achieve glycemic control may be partially due to the fact that oral therapy (e.g., sulfonylurea, metformin) does not appear to have a significant effect on progressively diminishing β-cell function,[10] although the thiazolidinedione class of insulin-sensitizing agents is currently under investigation as a diabetes-preventive agent.[11] By contrast, insulin therapy aimed at increasing basal insulin levels often ameliorates the effects of impaired β-cell function. Based on ACE and ADA guidelines, physicians should consider initiating insulin therapy in patients with A1C concentrations greater than 7.0% despite treatment with oral agents.[2,4,8]

Types of Insulin

Two formulations of insulin are available to control plasma glucose levels in patients with type 2 diabetes mellitus: human insulins (conventional/regular) and insulin analogs. Table 2 presents the time courses of action for available insulin preparations.[12] Human insulin is most useful for patients who have insulin allergies, severe insulin resistance caused by insulin antibodies, or lipoatrophy, as well as for patients who require intermittent insulin therapy (e.g., during pregnancy, acute infection, or myocardial infarction).[12]

Table 2. Time Courses of Action for Insulin Preparations

	Onset of Glucose-Lowering Action	Time to Peak Glucose-Lowering Action	Duration of Action
Mealtime insulins			
Short-acting			
Regular	30–60 min	2–5 h	5–8 h
Fast-acting			
Lispro, aspart or glulisine (analogs)	5–15 min	1 h	3–5 h
Basal insulins			
Intermediate-acting			
NPH or Lente	1–3 h	6–8 h	12–20 h
Long-acting			
Ultralente	2–4 h	8–12 h	18–28 h
Glargine (analog)	1–2 h	No pronounced peak	approx. 24 h
Fixed mixtures			
Humalog Mix 75/25	5–15 min	2–4 h	12–16 h
Novolog Mix 70/30	5–15 min	2–5 h	12–16 h
Human (70/30 or 50/50)	30–60 min	3–6 h	12–16 h

NPH, neutral protamine Hagedorn.

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