CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will individualize their decisions regarding insulin therapy in type 2 diabetes

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Starting insulin in patients with type 2 diabetes: An individualized approach

ABSTRACT

Because type 2 diabetes mellitus is a progressive disease, most patients eventually need insulin. When and how to start insulin therapy are not one-size-fits-all decisions but rather must be individualized. This paper reviews the indications, goals, and options for insulin therapy in type 2 diabetes.

KEY POINTS

In deciding a patient's hemoglobin A_{1c} goal and whether it is time to start insulin therapy, one should take into account the patient's age, life expectancy, concurrent illnesses, risk of hypoglycemia, and other factors.

When the target hemoglobin A_{1c} is not achieved with metformin or a two-drug regimen that includes metformin, the American Diabetes Association recommends adding a daily dose of basal insulin.

Eventually, preprandial bolus doses may need to be added to the insulin regimen to control postprandial blood glucose levels and hemoglobin A_{1c}.

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Insulin therapy is one of the most effective tools clinicians can use to help patients reach their individualized hemoglobin A_{1c} target. However, decisions about when and how to start insulin therapy have to be individualized to the needs and goals of each patient. Many insulin options are available, one of the most common being the addition of basal insulin to oral antidiabetic drugs. Although patients are often reluctant to start insulin, this reluctance can be overcome through patient education and hands-on training.

Here, we review hemoglobin A_{1c} targets, factors that determine when to start insulin therapy, and the different regimens that can be used.

MOST PATIENTS EVENTUALLY NEED INSULIN

Type 2 diabetes mellitus is a chronic progressive disease associated with insulin resistance, beta-cell dysfunction, and decreased insulin secretion. Consequently, most patients eventually require insulin therapy to reduce the risk of long-term complications.

The efficacy of therapy can be assessed by measuring hemoglobin A_{1c}, an important marker of the chronic hyperglycemic state. The hemoglobin A_{1c} value can be reported as a ratio (%) standardized against the results of the Diabetes Control and Complications Trial,[1] or as International Federation of Clinical Chemistry units (mmol/mol).[2] **Table 1** shows the relationship between hemoglobin A_{1c} and average glucose values.[3]

TABLE 1

Relationship between hemoglobin A_{1c} and average glucose values

Hemoglobin A_{1c}		Estimated average glucose value, mg/dL (95% confidence interval)
%	mmol/mol	
5	31	97 (76–120)
6	42	126 (100–152)
7	53	154 (123–185)
8	64	183 (147–217)
9	75	212 (170–249)
10	86	240 (193–282)
11	97	269 (217–314)
12	108	298 (240–347)

Based on information in Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ; A_{1c}-Derived Average Glucose Study Group. Translating the A_{1c} assay into estimated average glucose values. Diabetes Care 2008; 31:1473–1478.

WHAT IS AN APPROPRIATE HEMOGLOBIN A_{1c} TARGET?

The AACE and ADA are moving away from one-size-fits-all and toward individualized recommendations

The short answer is, "It depends."

Currently, the American Association of Clinical Endocrinologists (AACE) supports a hemoglobin A_{1c} goal of less than 6.5% for otherwise healthy patients but states that the goal should be individualized for patients with concurrent illnesses or at risk of hypoglycemia.[4]

On the other hand, the American Diabetes Association (ADA) recommends a higher hemoglobin A_{1c} target of less than 7% for most adults with type 2 diabetes mellitus.[5] This value was shown to be associated with a reduction in the microvascular and macrovascular complications of diabetes.

Yet when three large trials[6–8] recently compared intensive and standard glucose control regimens, tighter glucose control failed to improve cardiovascular outcomes. Moreover, in one of the trials,[7] patients receiving intensive treatment had a higher rate of all-cause mortality. Details:

- Action in Diabetes and Vascular Disease (ADVANCE): 11,140 patients; average hemoglobin A_{1c} levels 6.5% vs 7.3%[6]
- Action to Control Cardiovascular Risk in Diabetes (ACCORD): 10,251 patients; average hemoglobin A_{1c} levels 6.4% vs 7.5%[7]
- Veterans Affairs Diabetes Trial (VADT): 1,791 patients; average hemoglobin A_{1c} levels 6.9% vs 8.4%.[8]

Similarly, a 2013 Cochrane review[9] that included 28 randomized controlled trials concluded that intensive control (in 18,717 patients) did not decrease all-cause and cardiovascular mortality rates compared with traditional glucose control (in 16,195 patients), and it increased the risk of hypoglycemia and serious adverse events.

As a result, the ADA[5] states that a hemoglobin A_{1c} target less than 6.5% is optional for patients with a long life expectancy, short duration of diabetes, low risk of hypoglycemia, and no significant cardiovascular disease. The ADA further defines a hemoglobin A_{1c} goal of less than 8% for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and long-standing diabetes.

Therefore, the AACE and ADA are moving away from "one-size-fits-all" goals and toward individualizing their recommendations.

WHEN SHOULD INSULIN BE STARTED?

Physicians should consider the needs and preferences of each patient and individualize the treatment. The most recent recommendations from the ADA[5] stress the importance of a patient-centered approach, with multiple factors taken into account. These include the patient's attitude, expected compliance with treatment, risk of hypoglycemia, disease duration, life expectancy, and comorbidities, and the side effects of oral medications and insulin.

Compared with previous guidelines, there are fewer rules on how and when to start insulin therapy. But absolute and relative indications for insulin therapy should be considered in patients with the following:

Absolute indications for insulin

- Ketoacidosis or catabolic symptoms, including ketonuria
- Newly diagnosed type 2 diabetes with pronounced hyperglycemia (glucose ≥ 300 mg/dL or hemoglobin A_{1c} ≥ 10.0%) with or without severe symptoms, including weight loss, polyuria, or polydipsia[10]

TABLE 2

Blood glucose values to measure when initiating or modifying insulin treatment

Blood glucose measurement	Goal (mg/dL)	Indication and frequency of measurement	Intervention
Fasting	70–130	Monitor daily after initiating the basal insulin	Titrate the basal insulin, usually with 2–4 units every 2–3 days, to reach the fasting glycemic goal Check hemoglobin A_{1c} after 3 months
Preprandial	70–130	Monitor before each meal after initiating one or more doses of preprandial (bolus) insulin or if fasting glucose is at goal but hemoglobin A_{1c} remains elevated	Titrate the bolus insulin, usually with 2–4 units every 2–3 days, to reach the preprandial glycemic goal Check hemoglobin A_{1c} after 3 months
1–2 hours postprandial	< 180	Monitor after each meal if fasting and preprandial glucose are at goal but hemoglobin A_{1c} remains elevated	Titrate the bolus insulin

Adapted from information in Garber AJ, Abrahamson MJ, Barzilay JI, et al; American Association of Clinical Endocrinologists. AACE comprehensive diabetes management algorithm 2013. Endocr Pract 2013; 19:327–336 and American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014; 37(suppl 1):S14–S80.

- Uncontrolled type 2 diabetes mellitus despite using one, two, or more oral antidiabetic drugs or glucagon-like peptide 1 (GLP-1) receptor agonists
- Gestational diabetes
- Preference for insulin.

Relative indications for insulin

- Hospitalized for surgery or acute illnesses
- Advanced renal or hepatic disease
- Inability to afford the cost or tolerate the side effects of oral antidiabetic drugs and GLP-1 receptor agonists.

Depending on the situation, blood glucose is measured fasting, before meals, or after meals after initiating or adjusting insulin regimens (**Table 2**).

WHAT ARE THE INSULIN REGIMENS?

Basal insulin

In the early stages of type 2 diabetes, metformin alone or in combination with another oral antidiabetic drug or with a GLP-1 receptor agonist is often used along with healthy eating, weight control, and increased physical activity.

When the target hemoglobin A_{1c} cannot be achieved with one or two noninsulin drugs, the ADA suggests basal insulin be added to metformin or a two-medication regimen that includes metformin (**Table 3**). However, recent evidence suggests that combining a GLP-1 receptor agonist with basal insulin, in a regimen without metformin, is safe and improves glycemic control without hypoglycemia or weight gain.[11]

The ADA suggests basal insulin be added to metformin alone or a regimen that includes metformin

While a total daily dose of insulin of 0.1 to 0.2 units/kg could be initially used in patients with a hemoglobin A_{1c} level less than 8%, a higher dose of 0.2 to 0.3 units/kg is required if the hemoglobin A_{1c} level is between 8% and 10%. The dose can be titrated once or twice weekly if the fasting glucose is above the target level (usually < 130 mg/dL). If hypoglycemia develops (glucose < 70 mg/dL), the insulin dose should be reduced by 10% to 20%.[10]

Available basal insulins include glargine, detemir, and neutral protamine Hagedorn (NPH) (**Table 4**).[12–14] Because glargine and detemir offer better pharmacokinetic properties, less variability in response, and less risk of hypoglycemia, they are preferred over NPH.

TABLE 3

Medications that can be used with insulin in type 2 diabetes mellitus

FIRST MEDICATION
Metformin

SECOND MEDICATIONS

First-generation sulfonylureas
Tolbutamide
Chlorpropamide
Tolazamide

Second-generation sulfonylureas (preferred)
Glyburide
Glipizide
Glimepiride

Meglitinides[a]
Repaglinide
Nateglinide

Dipeptidyl peptidase-4 inhibitors
Sitagliptin
Saxagliptin
Linagliptin
Alogliptin

Glucagon-like peptide 1 agonists
Exenatide
Liraglutide
Exenatide ER
Albiglutide
Dulaglutide

Thiazolidinediones
Rosiglitazone
Pioglitazone

Alpha-glucosidase inhibitors[a]
Acarbose
Miglitol

Sodium-glucose cotransporter 2 inhibitors[a]
Canagliflozin
Dapagliflozin
Empagliflozin

[a] Listed only in the American Association of Clinical Endocrinologists' guidelines

Adapted from information in American Diabetes Association (ADA)[5] and American Association of Clinical Endocrinologists (AACE)[4] recommendations.

Glargine has a relatively constant plasma concentration over 24 hours, allowing once-daily dosing at any time during the day (**Figure 1**).[15] The dose should be taken at the same time every day. Detemir and NPH are usually taken once or twice daily.

Patients treated once daily should take the dose with the evening meal or at bedtime. Patients who require a twice-daily regimen can take the first dose with breakfast and the second one with the evening meal, at bedtime, or 12 hours after the morning dose.

The randomized Treat-to-Target trial,[16] in 756 patients, showed that both glargine and NPH, when added to oral therapy in patients with type 2 diabetes, achieve the target hemoglobin A_{1c}, but NPH is associated with more episodes of nocturnal hypoglycemia. Similar results were found when NPH was compared with detemir insulin.[17]

A Cochrane review[18] suggested that glargine and detemir are similar in efficacy and safety. However, detemir often needs to be injected twice daily, in a higher dose, and is associated with less weight gain. Furthermore, a meta-analysis of 46 randomized clinical trials[19] showed that the weight increase at 1 year is less in patients treated with basal than with twice-daily or prandial regimens.

A noninterventional longitudinal study[20] in 2,179 patients newly started on insulin showed that the mean weight increase at 1 year was 1.78 kg, and 24% of patients gained more than 5 kg. However, the factors independently associated with the weight gain were a higher hemoglobin A_{1c} at baseline, a higher insulin dose at baseline and at 1 year, and a lower baseline body mass index, but not the type of insulin regimen.

Currently, a new class of ultralong-acting basal insulins is being studied. Insulins in this class are approved in other countries, but the US Food and Drug Administration requires additional data for approval. Ultralong-acting insulins are expected to reduce the risk of hypoglycemia, specifically the risk of nocturnal episodes. Also, given their longer duration of action and stable steady-state pharmacokinetics, they will offer flexibility in the dose timing.[21]

Basal-bolus regimens

Basal insulin often does not control postprandial hyperglycemia. The need for multiple doses of insulin (including one or more prepandial doses) is suggested by postprandial glucose values above target (usually > 180 mg/dL) or by a hemoglobin A_{1c} above goal despite well-controlled fasting glucose levels. This usually becomes evident when the total daily dose

TABLE 4

Types of insulin

Type of Insulin	Onset	Peak	Duration	Cost [a]
Rapid-acting and short-acting				
Lispro	15–30 minutes	30 minutes–2.5 hours	3–6.5 hours	Vial (3 mL): $72.94 Pen (3 mL): $93.96
Aspart	10–20 minutes	40–50 minutes	3–5 hours	Vial: (10 mL): $243.89 Pen (3 mL): $94.23
Glulisine	25 minutes	40–50 minutes	4–5.3 hours	Vial (10 mL): $221.82 Pen (3 mL): $85.70
Regular Humulin R Novolin R	30–60 minutes	1.5–5 hours	6–8 hours	Vial (10 mL): $131.47
Inhaled regular insulin	1–5 minutes	12–15 minutes	3–4 hours	90 cartridges: $226.06–$278.59
Intermediate-acting and long-acting				
Neutral protamine Hagedorn (NPH) Humulin N Novolin N	1–2 hours	4–12 hours	14–24 hours	Vial (3 mL): $39.49 Pen (3 mL): $83.48 Vial (10 mL): $131.47
Detemir	1–2 hours	3–9 hours	6–23 hours (dose-dependent)	Vial (10 mL): $298.21 Pen (3 mL): $89.46
Glargine	1–1½ hour	No peak time; insulin is delivered at a steady level	11 to > 24 hours	Vial (10 mL): $298.21 Pen (3 mL): $89.46
Premixed				
Novolin 70/30	30–60 minutes	2–10 hours	18–24 hours	Vial (10 mL): $131.47
Humulin 70/30				Vial (3 mL): $39.49 Pen (3 mL): $83.48
Humalog 75/25	10–30 minutes	1–6 hours	14–24 hours	Vial (10 mL): $251.99 Pen (3 mL): $93.96
Novolog 70/30				Vial (10 mL): $251.99 Pen (3 mL): $93.96
Humalog 50/50				Vial (10 mL): $252.98 Pen (3 mL): $94.23

[a] The pricing data provide a representative average wholesale price and/or the average wholesale price from a single manufacturer of the brand product.

Adapted from information in Lexicomp Online (http://www.wolterskluwercdi.com/lexicomp-online/),[14] Pharmacist's Letter/Prescriber's Letter (www.PharmacistsLetter.com),[13] and Nuffer et al.[12]

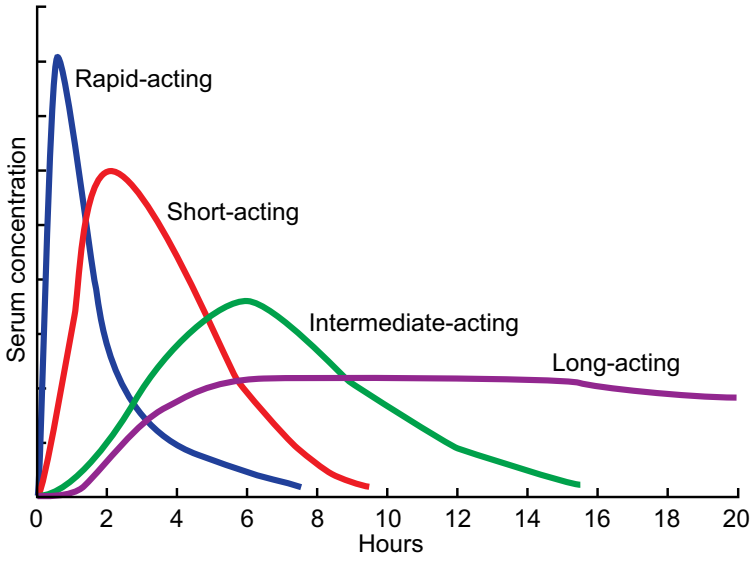

FIGURE 1. Approximate pharmacokinetic profiles of human insulin and insulin analogues. The relative duration of action of the various forms of insulin is shown. The duration varies widely both between and within persons.

Adapted from Hirsch IB. Insulin analogues. N Engl J Med 2005; 352:174-183. Copyright 2005, Massachusetts Medical Society.

Patients who are engaged in their care are more likely to succeed in their treatment

of basal insulin exceeds 0.5 units/kg. Patients newly diagnosed with diabetes who have a hemoglobin A_{1c} higher than 10% may also respond better to an initial basal-bolus regimen.

Available bolus insulins include lispro, aspart, glulisine, regular insulin, and the newly approved Technosphere inhaled regular insulin (**Table 4**).[12–14] They can be taken before each meal, and the total bolus dose usually represents 50% of the total daily dose.[22] Rapid-acting insulins have faster onset, shorter duration of action, and more predictable pharmacokinetics, which makes them preferable to regular insulin (**Figure 1**).[15] Inhaled insulin is another option, but it is contraindicated in patients with chronic obstructive pulmonary disease or asthma because of the increased risk of acute bronchospasm.[12]

Alternatively, the transition to a basal-bolus regimen can be accomplished with a single dose of bolus insulin before the main meal, using a dose that represents approximately 10% of the total daily dose. Additional bolus doses can be added later based on the glycemic control. The adjustment of the preprandial insulin dose is done once or twice weekly, based on the postprandial glucose levels.[10]

Premixed combinations of long- and short-acting insulins in ratios of 50% to 50%, 70% to 30%, or 75% to 25% can be considered in patients who cannot adhere to a complex insulin regimen. A propensity-matched comparison of different insulin regimens (basal, premixed, mealtime plus basal, and mealtime) in patients with type 2 diabetes revealed that the hemoglobin A_{1c} reduction was similar between the different groups.[23] However, the number of hypoglycemic episodes was higher in the premixed insulin group, and the weight gain was less in the basal insulin group.

While premixed insulins require fewer injections, they do not provide dosing flexibility. In other words, dose adjustments for premixed insulins lead to increases in both basal and bolus amounts even though a dose adjustment is needed for only one insulin type. Thus, this is a common reason for increased hypoglycemic episodes.

Continuous subcutaneous insulin infusion

A meta-analysis showed that continuous subcutaneous insulin infusion (ie, use of an insulin pump) was similar to intensive therapy with multiple daily insulin injections in terms of glycemic control and hypoglycemia.[24] Since both options can lead to similar glucose control, additional factors to consider when initiating insulin infusion include lifestyle and technical expertise. Some patients may or may not prefer having a pump attached for nearly all daily activities. Additionally, this type of therapy is complex and requires significant training to ensure efficacy and safety.[25]

WHAT IS THE COST OF INSULIN THERAPY?

A final factor to keep in mind when initiating insulin is cost (**Table 4**).[12–14] Asking patients to check their prescription insurance formulary is important to ensure that an affordable option is selected. If patients do not have prescription insurance, medication assistance programs could be an option. However, if a patient is considering an insulin pump, insurance coverage is essential. Depending on the manufacturer, insulin pumps cost about $6,000 to $7,000, and the additional monthly supplies for the pump are also expensive.

If patients are engaged when considering and selecting insulin therapy, the likelihood of treatment success is greater.[26–28]

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