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Using prandial insulin to achieve glycemic control in type 2 diabetes

A stepped approach to postprandial hyperglycemia—including prandial insulin—is key

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Practice recommendations

- A stepwise approach to antidiabetic therapy allows for the treatment to change in response to disease progression. This usually means beginning with oral agents and adding insulin as required (**B**).
- Treatment strategies must address both fasting and prandial hyperglycemia because prandial hyperglycemia has been shown to be an independent risk factor for cardiovascular events and mortality (**B**).

Strength of recommendation (SOR)

A Good-quality patient-oriented evidence
B Inconsistent or limited-quality patient-oriented evidence
C Consensus, usual practice, opinion, disease-oriented evidence, case series

More than 80% of patients with type 2 diabetes—including more than a third of patients with good metabolic control—have excessive postprandial hyperglycemia.[1] That's unwelcome news for the 20 million Americans with type 2 diabetes, especially when you consider that postprandial hyperglycemia is a strong independent risk factor for all-cause mortality and cardiovascular events.[2–5]

To help our type 2 diabetes patients gain ideal control, we need to do at least 2 things better:

1. Measure and act on glycosylated hemoglobin (A_{1c}) levels.
2. Take a stepped approach to glycemic control, making full use of prandial insulin.

A_{1c} levels and the important role they play

Analysis of A_{1c} is the "gold standard" for monitoring glycemic control in patients with diabetes because it provides an indication of mean plasma glucose levels during the preceding 120 days.[6] The relative contribution of fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) to A_{1c} levels is a dynamic function of the extent of day-long hyperglycemia; FPG has a greater influence at higher A_{1c} levels and PPG has a predominant role at lower A_{1c} levels.[7]

The relationship between hyperglycemia, as measured by A_{1c}, and increased morbidity and mortality (including cardiovascular events) was demonstrated several years ago in the United Kingdom Prospective Diabetes Study (UKPDS).[8] Interestingly, several studies have also found that fasting glucose levels alone are not a reliable predictor for hyperglycemia-related morbidity or mortality,

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whereas postprandial hyperglycemia, as noted in the introduction, is a strong independent risk factor for all-cause mortality and cardiovascular events.[2–5]

Continued management of A_{1c} through tight control of both FPG and PPG may therefore improve patient long-term health outcomes. A_{1c} should be evaluated every 3 to 6 months, and appropriate changes to the patients' treatment regimens should be made accordingly.

An algorithm for the stepwise approach

We typically use oral antidiabetic drugs typically are used as initial therapy for patients with newly diagnosed type 2 diabetes, especially those with initial A_{1c} levels of 6.0% to 8.0%.[9] Three recent publications[10–12] provide an excellent analysis of the rationale for combination therapy to address multiple physiologic defects, as well as the relative efficacy of agents.

In 2006 the American Diabetes Association (ADA) and the European Association for the Study of Diabetes published a consensus statement that presented an algorithm for the initiation and adjustment of type 2 diabetes therapy (**FIGURE**).[13] In this evidence- and experience-based treatment algorithm, the authors emphasize the achievement and maintenance of normal glycemic goals, initiating therapy with lifestyle intervention and metformin (Glucophage), not delaying therapy and transitioning to new regimens when glycemic targets are not achieved, and adding insulin therapy early to the regimens of patients who are not meeting glycemic targets.[9,13]

You may also consider newer therapeutic options not included in the ADA's 2007 treatment guidelines.[14] Incretin mimetics and dipeptidyl-peptidase IV (DPP-IV) inhibitors are 2 new classes of antidiabetic agents that are effective for patients with type 2 diabetes. (See **"2 new classes of antidiabetic agents: Incretin mimetics and DPP-IV inhibitors"**[15-22] on page 738.) Most patients with type 2 diabetes will, however, eventually require insulin therapy to maintain optimal glycemic control.[23]

FAST TRACK

The ADA's stepped approach begins with lifestyle interventions and oral agents, and progresses to insulin if glycemic goals are not met

Advancement to insulin therapy

Basal insulin replacement achieves glycemic control

The addition of once-daily basal insulin to oral antidiabetic drug regimens is a simple way to introduce insulin therapy and achieve glycemic control. (See **"A guide to basal insulin dosing and titration"**[14,24-28] on page 739.)

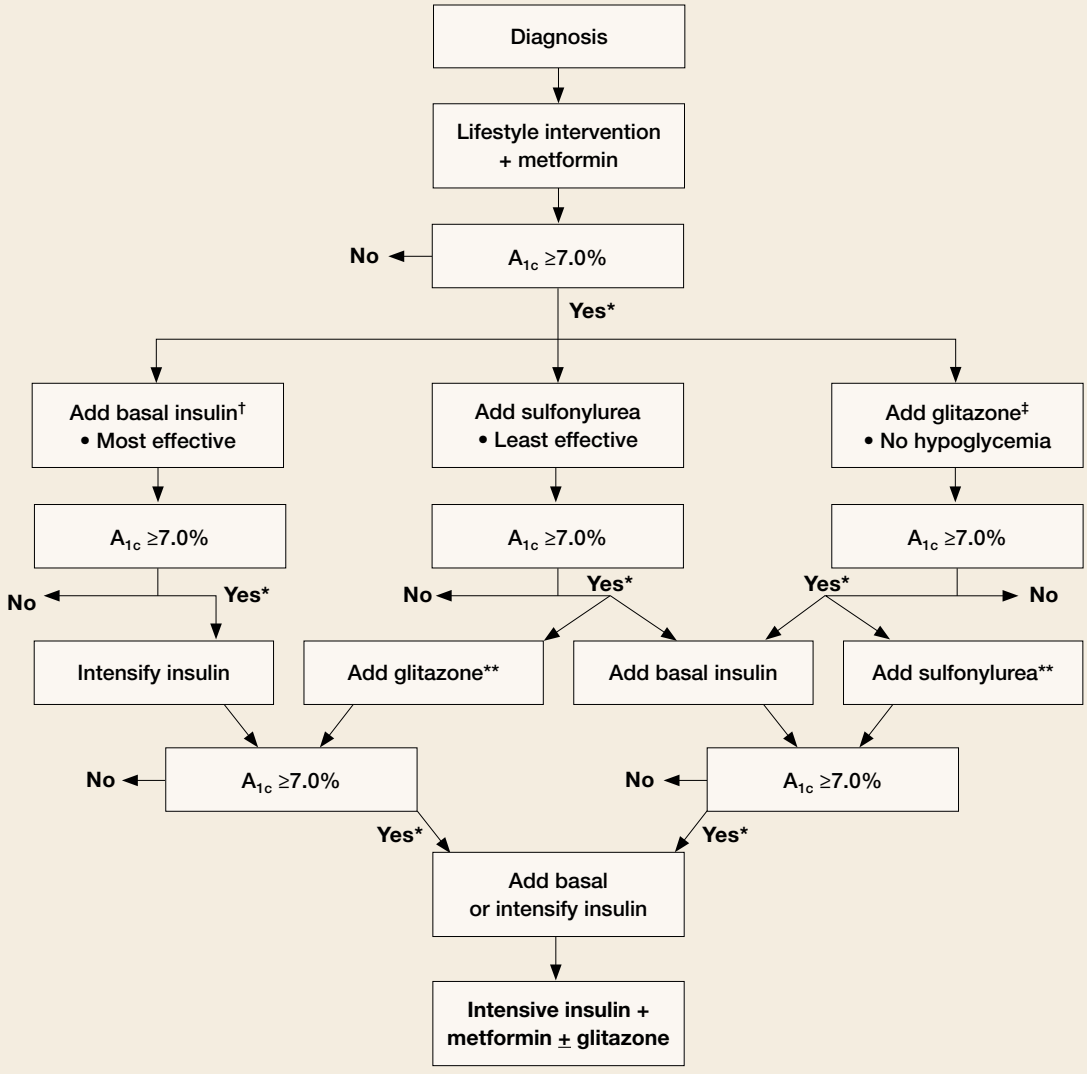
- In a randomized, parallel, multicenter study, treatment with once-daily insulin glargine (Lantus) or neutral protamine Hagedorn (NPH) insulin (Humulin, Novolin) added to preexisting oral antidiabetic drug regimens for 756 patients with inadequately controlled type 2 diabetes (A_{1c} >7.5%) effectively achieved the goal A_{1c} of ≤7.0% for most patients. More patients in the insulin glargine group were able to reach goal without experiencing any nocturnal hypoglycemia, compared with those in the NPH group (33.2% vs 26.7%, $P<.05$).[24]
- A similar study used a forced-titration algorithm to compare NPH insulin with insulin detemir (Levemir).[26] This study demonstrated that a similar reduction in A_{1c} could be achieved with insulin detemir and NPH insulin over 24 weeks (1.8% and 1.9%, P=ns), but weight gain and nocturnal hypoglycemia incidence were significantly lower with insulin detemir compared with NPH insulin (1.2 kg vs 2.8 kg, and 160 vs 349 events, respectively, $P<.001$ for both).

Prandial insulin is as effective as carbohydrate counting

If a patient doesn't reach his or her A_{1c} targets despite appropriate titration of the basal insulin dose, injections of a rapid-acting insulin analog at mealtime

FIGURE

An evidence-based algorithm for achieving normal glycemic goals in patients with type 2 diabetes



Note: Reinforce lifestyle intervention at every visit.

*Check A_{1c} every 3 months until <7% and then at least every 6 months.

†At A_{1C} >9%.

‡At A_{1C} ≤8%.

**Although 3 oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense.

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may be necessary. You can add rapid-acting insulin to the regimen, starting with 1 injection at the largest meal of the day and then adding an injection at additional meals as needed.

• A typical starting dose of rapid-acting prandial insulin (insulin aspart [NovoLog], insulin glulisine [Apidra], or insulin lispro [Humalog]) would be 5 to 10 U per meal.[29]

• The range of daily dose, when used at 3 meals per day, would be 0.2 to 0.5 U/kg per day (ie, 0.1 to 0.15 U/kg per meal).[29] For a patient who weighs 100 kg, that would mean 20 U (6–7 units before each meal) per day.

CONTINUED

2 new classes of antidiabetic agents: Incretin mimetics and DPP-IV inhibitors

Incretin mimetics

Incretins, such as glucagonlike peptide-1 (GLP-1), enhance glucose-dependent insulin secretion by the pancreatic beta cells and exhibit other antihyperglycemic actions after release into circulation by the gut.

Exenatide (Byetta) is the first agent in this class to be approved by the Food and Drug Administration for use in type 2 diabetes. Exenatide may be used in combination with oral therapy (a sulfonylurea and/or metformin) by patients who have not achieved adequate glycemic control on oral therapy alone. Exenatide mimics the antihyperglycemic actions of GLP-1 but maintains a prolonged duration of action compared with endogenous GLP-1.[15] This agent effectively addresses postprandial hyperglycemia by restoring a rapid postprandial insulin response; consider it when reduction of postprandial glycemic excursions is required.

When injected twice daily (before morning and evening meals), exenatide reduces hyperglycemia and promotes satiety, which in turn reduces caloric intake and body weight. In a recent study, exenatide achieved reductions in A_{1c} (1.11%) similar to those observed with insulin glargine when it was added to sulfonylurea/metformin combination therapy for patients with type 2 diabetes.[16] Exenatide reduced fasting plasma glucose (FPG) to a greater degree, whereas insulin glargine had a greater effect on FPG. This suggests that a basal insulin may be more appropriate when FPG levels are elevated (ie, patients with A_{1c} levels >8.0%) and exenatide may be more useful for patients with A_{1c} levels <8.0%, when elevated PPG levels are predominant.[17] However, some patients with A_{1c} levels >8.0% also may benefit from such intervention.

Liraglutide, another incretin mimetic, is in development for the treatment of type 2 diabetes. Liraglutide is a long-acting GLP-1 analog in phase 3 development for once-daily treatment of type 2 diabetes. The mechanism of action is similar to that of exenatide, but with a longer duration of action. Liraglutide may be suitable for once-daily administration. Initial data indicate that liraglutide improved glycemic control while providing modest weight loss for patients with type 2 diabetes.[18] (Available online at: www.novonordisk.com/science/pipeline/rd_pipeline.asp. Accessed August 2, 2007.)

DPP-IV inhibitors

A new class of oral antidiabetic agents, DPP-IV inhibitors slow the degradation of incretin hormones, allowing these hormones to stimulate insulin secretion and decrease glucagon levels in the circulation in a glucose-dependent manner.[19,20]

Sitagliptin (Januvia) has been approved for use as monotherapy or in combination with metformin, pioglitazone, or rosiglitazone for the treatment of type 2 diabetes. Once-daily sitagliptin improves glycemic control, reducing A_{1c} from 0.4% to 1.1% and decreasing fasting plasma glucose from 12 to 17 mg/dL and 2-hour postprandial glucose from 49 to 62 mg/dL in clinical trials. It is well-tolerated,[21,22] but its long-term efficacy and safety are unknown.

Vildagliptin (Galvus), another DPP-IV inhibitor has completed phase 3 testing and is pending FDA approval at this time. (Available online at: www.diabeteshealth.com/read/2007/03/16/5039.html. Accessed August 2, 2007.)

Recent data indicate that a simple treatment algorithm based on preprandial glucose patterns can be as effective as carbohydrate counting for the dose titration of prandial insulin.[30] In this 24-week study, insulin glulisine was added to basal-prandial insulin therapy, with insulin glargine as the basal insulin component. Glulisine was adjusted to target using either a simple algorithm of adding 1, 2, or 3 U based on premeal glucose patterns or standard carbohydrate counting. The carbohydrate counting–based dose adjustment and the algorithm-based titration treatment arms achieved similar A_{1c} reductions. However, patients using the simple algorithm experienced significantly less symptomatic hypoglycemia (P=.02).

A guide to basal insulin dosing and titration

- **Initiate basal insulin** with a 10 U once-daily dose of insulin glargine, insulin detemir, or NPH insulin.[24] (Note: NPH insulin and insulin detemir may require twice-daily dosing.)[25]
- **Titrate weekly** to a target fasting plasma glucose [FPG] of ≤100 mg/dL based on the average self-monitored FPG values from the preceding 2 days as follows:[24]
  - If FPG is ≥180 mg/dL, increase insulin dosage by 8 U/d.
  - If FPG is 140–180 mg/dL, increase insulin dosage by 6 U/d.
  - If FPG is 120–140 mg/dL, increase insulin dosage by 4 U/d.
  - If FPG is 100–120 mg/dL, increase insulin dosage by 2 U/d.
  - If FPG is <72 mg/dL at any time during the week, do not increase insulin dosage.
  - If FPG is <56 mg/dL, decrease insulin dosage by 2–4 U/d.

Keep in mind…

- A similar titration schedule to the one described here was effective in a study with insulin detemir and NPH insulin.[26]
- An alternative titration strategy to the one here would be to increase basal insulin dose by 2 U every 3 days to reach an FPG level of ≤100 mg/dL.[27,28]
- Less stringent A_{1c} goals may be appropriate for patients with limited life expectancies, very young children, the elderly, and individuals with comorbid conditions.[14]

Rapid-acting analogs allow more flexible administration

Prior to the development of rapid-acting insulin analogs, regular human insulin (RHI) was the only available insulin suitable for prandial glycemic control. However, it had significant limitations, including the need for it to be injected 30 to 45 minutes before eating (and the poor compliance with this requirement), variability in peak levels (between patients and with the same patient), variability in absorption based on injection site, and frequent episodes of hypoglycemia.[31,32]

Newer rapid-acting insulin analogs such as insulin aspart, insulin glulisine, and insulin lispro demonstrate improved pharmacokinetic profiles with more rapid onset, faster time to peak activity, and shorter duration of action than RHI.[32,33] These rapid-acting analogs allow administration right before or right after a meal, resulting in improved glycemic control without increased hypoglycemia or weight gain.[34,35] Whereas the rapid onset of action of these analogs allows for administration 5 to 15 minutes before a meal, the patient can administer insulin glulisine within 20 minutes of the start of the meal.[36] The addition of just 1 dose of prandial insulin to existing basal insulin plus oral antidiabetic drug therapy offers patients a substantial benefit.[37]

A new option: Inhaled insulin

The US Food and Drug Administration recently approved an inhaled prandial insulin. Research has shown that it effectively addresses postprandial glucose excursions for patients with type 2 diabetes.[38,39] A 12-week trial comparing A_{1c} levels among patients switched to inhaled insulin (Exubera) before meals (n=76) or rosiglitazone (Avandia) 4 mg twice daily (n=69) found that inhaled insulin reduced A1c to a greater degree than rosiglitazone (–2.3% vs –1.4%); however, patients receiving inhaled insulin experienced a greater incidence of hypoglycemia (0.7 vs 0.05 episodes per subject-month).[39]

Inhaled insulin can be used as monotherapy or in conjunction with oral

FAST TRACK

Adding just 1 prandial dose to a regimen of basal insulin and oral anti-diabetic drugs offers substantial benefits

TABLE

How to use sensitivity factors to calculate 24-hour insulin need

CHARACTERISTIC	DOSAGE (U/KG)
Phenotype	
Normal weight	
Extremely physically active	0.3 baseline
Moderately physically active	0.4 baseline
Minimally active	0.5 baseline
Obese	
Extremely physically active	0.5 baseline
Moderately physically active	0.6 baseline
Minimally active	0.8 baseline
Renal failure	Subtract 0.2
Coexisting illness raising risk of hypoglycemia	Subtract 0.2
Eating habits ("big eater")	Add 0.1
New-onset type 1 diabetes, <30 years of age	0.3 baseline

Reprinted with permission from Leahy, *Insulin Therapy* 2002.[29]

FAST TRACK

Inhaled insulin is an appealing option for patients who are reluctant to begin insulin therapy because of the injections

agents or a long-acting basal insulin. Inhaled insulin has a rapid onset of action (within 10–20 minutes, comparable with rapid-acting insulin analogs) and a duration of glucose-lowering activity of approximately 6 hours (comparable with RHI).[40] This is useful for patients reluctant to begin insulin therapy because of injections; however, you will need to closely monitor hypoglycemia.

Basal-prandial insulin in new type 2 diabetes

In certain cases, it may be more appropriate to initiate insulin therapy using a basal-prandial regimen that includes injections of prandial insulin with each meal of the day. Such cases include patients with newly diagnosed type 2 diabetes who have A_{1c} levels >10.0%, or insulin-naive patients on oral antidiabetic drug regimens who have A_{1c} levels >8.5%.[25]

You can calculate the starting total 24-hour insulin dosage for both the basal and prandial insulin components by multiplying body weight in kg by a factor based on the patient's estimated insulin sensitivity (**TABLE**).[29]

Once you have this 24-hour insulin dose, you'll then need to calculate the dose of basal insulin, which is 50% of the 24-hour total insulin dose, administered once daily. The remaining 50% of the total 24-hour dose provides prandial insulin coverage and is usually administered as follows:

- 30% to 40% at breakfast
- 30% at lunch
- 30% to 40% at dinner

Patients will need to adjust prandial insulin doses based on self-monitored blood glucose values.

Premixed insulin formulations

You should have your patients administer basal-prandial insulin as separate injections (eg, insulin glargine and insulin glulisine,[30] or insulin detemir and insulin aspart[25]). The premixed (NPH based) formulations provide fixed doses of an intermediate- or long-acting insulin combined with a short-acting insulin. Although this method may be convenient to administer, it is more rigid and may not account for mealtimes and exercise. As a result, insulin levels will not match physiological insulin and thus, the risk for hypoglycemia increases. Another disadvantage is that adjustments to the dose based on self-monitored glucose levels are not possible with premixed formulations.[41]

Separating the basal and prandial insulin components allows the insulin regimen to be adapted to an individual's needs, thereby providing glycemic control with less propensity for hypoglycemia. ■

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Disclosure

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FAST TRACK

Patients with newly diagnosed type 2 diabetes and A_{1c} levels over 10% will benefit from a basal-prandial regimen

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