As the number of patients with diabetes mellitus (DM) grows, largely due to an epidemic of obesity, the number of patients treated with insulin will also increase. Most patients with type 2 DM progressively lose β-cell function. Although earlier diagnosis will change these data, newly diagnosed patients with type 2 DM have less than 50% of normal insulin secretion at diagnosis, and less than 25% of normal insulin secretion 6 years after diagnosis (see Figure 4 in the accompanying article). This decline in β-cell function explains the initial and secondary failure of oral agents in patients with type 2 DM. Meticulous glucose control decreases long-term microvascular complication rates. In patients who have had recent myocardial infarction, aggressive insulin therapy aiming for tight glucose control is associated with reduced mortality. These data have led the American Diabetes Association to recommend that patients aim for hemoglobin (Hb) A1C levels of less than 7%. A 1990s “Diabetes Report Card for the United States” found that only 29% of patients with DM had their HbA1C tested in the previous year. Of those patients, 18% had an HbA1C level of 9.5% or higher (poor control), only 43% had an HbA1C level of less than 7%, and the median HbA1C level was 7.5%.

The addition of bedtime injection (9 PM) intermediate- or long-acting insulin to oral agents have significantly improved glycemic control in patients with uncontrolled type 2 DM, but clinicians and patients often delay starting insulin therapy. In the past, hypoglycemia has been the main concern of physicians aiming for tight glycemic control. However, a better understanding of physiologic insulin replacement with basal and prandial insulins simplifies insulin dosing and adjustment. The truly basal insulin analogue, insulin glargine, and the rapid-acting insulin analogues, insulins lispro and aspart, have further improved physicians' ability to match patients' insulin needs. Since physiologic insulin replacement can improve control while causing fewer episodes of hypoglycemia, primary care clinicians should become familiar with these regimens, which are easier to use than many patients and clinicians realize. In our own clinical experience, the perceived complexity of insulin regimens, the difficulty in finding straightforward practical clinical information and resources (BOX 1), and misconceptions about the cost and risks of insulin therapy are major barriers to physician and patient use of insulin. While the main purpose of complex insulin dose adjustments and supplements (see accompanying article) is to allow maximum flexibility and to improve glycemic control, a simple conceptual approach to insulin use (eg, basal-prandial) and understanding associated tools, such as carbohydrate counting, allows patients and physicians to improve diabetes care.

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Box 1. Resources for Primary Care Physicians and Patients

Insulin Administration
American Diabetes Association (ADA)
Published in: Diabetes Care. 2002;25:S112-S115
Contains tips about insulin:
- Do not mix glargine with other insulin products
- When mixing rapid-acting insulin and intermediate-acting insulin, inject within 15 minutes
- Syringe reuse acceptable but meticulous attention to cleanliness is needed; small needles (30 gauge) develop barbed tips easily
- Insulin pens improve dose accuracy
- Injection site should be clean, but wiping with alcohol not needed (insulin injections may be given through clothing)
- Injection site rotation reduces lipoatrophy but increases variability of absorption (abdomen region has a faster absorption rate than the arm, which is faster than the leg; exercise increases rate of absorption)

Clinical Practice Recommendations
American Diabetes Association
Contains: ADA practice guidelines
- Available as full text at http://care.diabetesjournals.org or via ADA Web site
- Includes guidelines for treatment of type 1 and type 2 diabetes mellitus, as well as multiple practical topics

Clinical Guidelines
American Association of Clinical Endocrinologists
National Diabetes Education Program

CLINICAL CASES

Patient 1
A 58-year-old man presented 8 years ago with type 2 DM. He was taking glipizide 2.5 mg twice daily, with an HbA1c level of 7.8%. He initially lost 10 lb (4.5 kg) but during the subsequent 6 years, his HbA1c level rose to 10% despite increasing glyburide to 10 mg twice daily.

This case illustrates secondary failure of an oral agent. He will require insulin to achieve an HbA1c level of less than 7%. In general, single oral agents lower HbA1c levels by 1% to 2% and combination therapy lowers HbA1c by 2%. Thus, patients with an HbA1c level of 9% or higher who are receiving monotherapy are very unlikely to reach a target HbA1c level of less than 7%. Unfortunately, like many other patients, patient 1 was reluctant to take insulin. Therefore, metformin, 1000 mg twice daily, was added to his regimen and glyburide was reduced to 5 mg, twice daily. He did not follow-up until 2 years later when his HbA1c level was 11% while using this regimen.

In patients with residual insulin production, using bedtime neutral protamine Hagedorn (NPH; isophane insulin) or insulin glargine to provide basal insulin while continuing an oral agent, such as glyburide or metformin, to boost prandial glucose disposal, is an effective strategy. Limited data show that sulfonylureas (SUs) added to insulin produce mildly better glycemic control with fewer episodes of hypoglycemia than insulin alone. A major study comparing bedtime NPH plus metformin, bedtime NPH plus glyburide, glyburide plus metformin, and NPH alone in the morning and at bedtime found that bedtime NPH and metformin produced the best control, the fewest hypoglycemic episodes, and the least weight gain. When adding insulin to a regimen, bedtime basal insulin is a reasonable first step, especially for a patient who is reluctant to start insulin therapy. A sensible starting dose is 10 to 20 U of NPH, but 40 to 60 U or more is typically required (Box 2). The duration of disease for patient 1 suggests that he also may need prandial insulin to achieve optimal control.

Cost varies by drug and by dose. Oral agents, even generic, used in combination are often more expensive than insulin products. Using generic pricing, the estimated cost of the regimen for patient 1 (glyburide, 5 mg twice daily, and metformin 1000 mg twice daily) is $67 per month (www.drugstore.com, as of January 2003). For a starting regimen of insulin of 15 U/d, the cost is approximately $34 per month for NPH or approximately $54 per month for insulin glargine, including syringes and alcohol wipes. If patient 1 were to continue using glyburide or metformin, this would add $12 or $55 per month. Finally, the cost of a treatment program is strongly influenced by the frequency of capillary blood glucose (CBG) testing ($0.65 per test). Since basal insulin regimens can often be initiated and maintained based on fasting CBG levels, they can have relatively low monitoring costs.

Patient 2
A 68-year-old Filipina woman with type 2 DM and congestive heart failure has been taking 70% NPH/30% regular (70%N/30%R or 70/30) insulin for 4 years. She takes 16 U every morning and 12 U every evening. Her fasting CBG levels are 120 to 150 mg/dL (6.7-8.3 mmol/L) but she develops hypoglycemia if she eats lunch late. Her predinner CBG levels are 180 to 240 mg/dL (10.0-13.3 mmol/L). She walks every afternoon to try to control her predinner glucose level. Her diet is high in rice and other complex carbohydrates. Her HbA1c level is 8.5%.

Options for insulin therapy for patient 2 include using split-mix (the pa-
tient mixes the insulin) NPH/R or Ul-
tralente (insulin zinc extended) (UL)/R,
but premeal and nocturnal hypoglyce-
mia are common if meal timing is not
precise (eg, late lunch [see Figure 2 in
accompanying article]). Premixed 70%
N/30% R insulin is more convenient but
it has the same problems as the split-
mix regimen because the tail of the regu-
lar insulin action overlaps with the peak
NPH action in late morning and at night.
In our clinical experience, many pa-
tients receiving twice-daily NPH insu-
lin and prandial regular insulin, who are
aiming for or who appear to have good
glycemic control, have wide fluctua-
tions of glucose levels with very high glu-
cose levels immediately after breakfast
dinner and hypoglycemia before
lunch and at night. This risk of night-
time hypoglycemia is the reason for the
traditional bedtime snack. The pre-
mixed, neutral protamine lispro (insu-
lin lispro protamine, NPL)/lispro (L) in-
sulin analogue combination (75% NPL/
25% L) is a good option for patients with
high-carbohydrate diets or who experi-
ence prelunch hypoglycemia. Insulin
NPL has a peak similar to that of NPH,
but the shorter duration of action of in-
sulin lispro, compared with regular in-
sulin, means less overlap (Figure 1) and
thus reduced risk of hypoglycemic epi-
sodes.13-15

Patient 2 refused basal/prandial in-
sulin because of the additional injec-
tions required. Using twice-daily 75%
NPL/25% L, at the same dose improved
her HbA1c levels from 8.5% to 6.2% with
fewer episodes of hypoglycemia because
this regimen better matched her needs.
Controlled trials have not shown this
magnitude of benefit when switching
from regular insulin to insulin lispro
with meals, and more careful timing of
injection of split-mix NPH and regular
insulin (rather than premixed) might
accomplish the same benefit, but many
patients cannot attain and sustain that
level of precision. Finally, most patients
with type 2 DM need 1 U/kg or higher
to obtain an HbA1c level less than
7%.16-18 This patient’s excellent con-
tral while receiving low doses of insu-
lin is unusual, possibly reflecting her
high ethnic risk of type 2 DM at a low
body mass index (27 kg/m²), a rela-
tively early switch to insulin therapy,
and her vigorous walking program.

We have recently seen increasing con-
fusion regarding insulin prescription-
writing practices. Traditionally, many
physicians use the abbreviations “R” for
regular, “N” for NPH, or “L” for Lente
(insulin zinc). However, “L” can now
mean Lente, Lantus (Aventis Pharma-
aceuticals Inc, Bridgewater, NJ), or lis-
pro; “N” can mean “NovoLog” (Novo
Nordisk, Princeton, NJ), NPL, or NPH.
Thus, we advocate writing out the insu-
lin name in full. Furthermore, use of the
abbreviation “U” for units may be mis-
interpreted as a zero, for example, 5 U
translated to 50, if not written clearly.

Patient 3
A 76-year-old woman with type 2 DM
takes 70% N/30% R insulin, twice daily.
Despite multiple discussions and in-
termittent good glycemic control for
several months at a time (HbA1c range,
7.2%-8.6%), her adherence is affected
by her schedule. She prefers to get up
after 10 AM some days and her meal
schedule is very erratic, but she usu-
once a day and causes fewer episodes of hypoglycemia if patients already have reasonable glycemic control. As depicted in the figure, the additive effect of the insulin profile explains why patients would experience episodes of evening or nighttime hypoglycemia and fasting hyperglycemia. Arrows indicate insulin injection; NPH, neutral protamine Hagedorn (isophane insulin).

This patient’s erratic schedule and patterns of insulin use have resulted in insulin stacking, which explains her poor control and evening hypoglycemia (FIGURE 2). The concept of “basal-prandial” physiologic insulin dosing (see Figure 3 in accompanying article) often helps improve patients’ understanding of their diabetes, significantly increases flexibility for patients since they can change their meal times or skip meals, and can yield better glucose control. Traditionally, insulin regimens use two-thirds intermediate- or long-acting and one-third short-acting insulin. Although carbohydrate counting adds invaluable in training patients in self-management skills. Help from a diabetes educator is invaluable in training patients in self-management skills.

**Patient 4**

A 37-year-old woman with type 1 DM who takes metoclopramide for gastroparesis develops nausea, vomiting, and epigastric pain. She uses an insulin pump with insulin lispro (basal 0.9 U/h, prandial 1.8 U per premeal carbohydrate). She eats an early dinner. She becomes hypoglycemic every few days, commonly in the evening.

This patient’s erratic schedule and patterns of insulin use have resulted in insulin stacking, which explains her poor control and evening hypoglycemia (FIGURE 2). The concept of “basal-prandial” physiologic insulin dosing (see Figure 3 in accompanying article) often helps improve patients’ understanding of their diabetes, significantly increases flexibility for patients since they can change their meal times or skip meals, and can yield better glucose control. Traditionally, insulin regimens use two-thirds intermediate- or long-acting and one-third short-acting insulin. Although carbohydrate counting adds invaluable in training patients in self-management skills.
1 U per 10 g of carbohydrate). She reports frequent episodes of hypoglycemia and has been unable to take her oral medications. She is admitted to the hospital for an esophagogastroduodenoscopy the next day.

Long-term management of patients with type 1 DM using insulin pumps is usually best done by a specialty care team. However, continuing patients on their own pumps, for tests or short hospitalizations when they need to be fasting, is usually the easiest treatment plan. Their basal infusion is used alone when they are fasting and it is adjusted based on usual CBG monitoring. Basal needs are affected by insulin resistance from endogenous stress cortisol or medications and, typically, by decreased physical activity. Patients’ prandial insulin needs vary depending on their food intake.

Patient 5
A 70-year-old woman with type 2 DM presents with headache, myalgia, and sweats. Results of the evaluation show giant cell arteritis, and prednisone 60 mg/d is started. Her diabetes medication is glyburide, 7.5 mg/d. Typical fasting CBG levels are 100 to 130 mg/dL (5.6-7.2 mmol/L) and predinner levels are 120 to 150 mg/dL (6.7-8.3 mmol/L). Her HbA1c level is 7.2%. She asks how she should manage her diabetes while taking prednisone.

In persons taking corticosteroids, the primary defect is impaired disposal of glucose after meals. Corticosteroids increase gluconeogenesis, suppress insulin secretion, and decrease peripheral uptake of glucose. It is likely that in patient 5, her current postprandial CBG levels are 200 mg/dL (11.1 mmol/L) or higher. The usual goal in patients with steroid-induced or steroid-aggravated DM is to prevent glycosuria and symptoms of DM. The American Diabetes Association recommends fasting CBG levels lower than 110 mg/dL (6.1 mmol/L) and postprandial CBG levels lower than 180 mg/dL (10.0 mmol/L).23 Patients who already have DM should increase self-monitoring, ideally collecting baseline data 1 to 3 days before starting predni-