Type 2 Diabetes: What to Do When the Pills Don’t Work

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ABSTRACT

The incidence of type 2 diabetes mellitus in the United States has increased 61% from 1990; the disease now affects 6.5% of the population. Large-scale and long-term studies of patients with type 1 and type 2 diabetes conducted in both North America and the United Kingdom have found intervening to assure glycemic control by modifying lifestyle and using oral hypoglycemic agents and/or insulin can prevent devastating microvascular complications. This paper reviews the goals of therapy as well as a treatment strategy that begins with nonpharmacologic therapies and progresses to oral agents and insulin when necessary. Barriers to achieving adequate control are discussed. These obstacles may include: errors in diagnosis, problems with adherence due to medication side effects or unrealistic management plans, and natural history of the disease. The most recent evidence on insulin treatment will be presented, along with a suggested titration schedule based on home blood glucose monitoring.


A GROWING EPIDEMIC

More than 11 million people in the United States have been diagnosed with diabetes, and it is estimated that anywhere from another 6 million to as many as 12 million individuals have undiagnosed diabetes.1 Of even greater concern is that approximately one half of all people will already have some diabetes-related complications by the time they receive a diagnosis.2 A telephone survey conducted by the US Behavioral Risk Factor Surveillance System (BRFSS) found the prevalence of diagnosed diabetes rose dramatically, from 4.9% in 1990 to 6.5% in 1998, an increase of 33% in that 8-year period. Prevalence rose nearly another 10% between 1998 and 1999. The 2001 survey showed a further increase to 7.9%, a 61% increase since 1990.3 Intimately linked to the escalation in diabetes cases is the alarming rise in the prevalence of obesity among Americans. According to data from the BRFSS, diabetes increased by approximately 9% with every kilogram increase in self-reported weight. These increases have been observed in both sexes, all ages, and all ethnic and socioeconomic groups.4

The morbidity and mortality that result from complications of diabetes (cardiovascular and renal disease, blindness, amputations, and premature death) carry a high price, physically and financially. Based on data gathered by the American Diabetes Association (ADA), the total cost of diabetes in the United States, in terms of medical care and services, as well as the indirect costs of time lost from work due to short-term and permanent disability, is estimated to be $98 billion.5 Early, accurate diagnosis and effective management of diabetes—especially type 2 diabetes, which accounts for 90% to 95% of all cases—must be a priori-
ty for primary care clinicians. Few diseases provide so
great a challenge, perhaps because of inaccurate diag-
nosis, changing treatment goals, problems with com-
pliance and medications, and the natural progression
of the disease itself.

**Classification and Pathophysiology**

In 1997, the ADA reclassified diabetes into
everal categories. Previously, the classification sys-
tem was confusing and appeared to be based on
the age of the patient (juvenile- vs adult-onset) or
on how the patient was being treated (insulin-
dependent vs non-insulin-dependent). The new
system is based on etiology. What was previously
known as insulin-dependent diabetes or juvenile-
onset diabetes is now termed type 1 diabetes. Type
1 diabetes affects approximately 5% of those with
diabetes. Another small percentage of cases are
pregnancy related or arise from specific genetic con-
ditions or from infections, are secondary to other
illnesses, or are iatrogenic (surgically or pharma-
coleologically induced). Most people with diabetes
have type 2 diabetes (previously known as non-insulin-
dependent diabetes), characterized by insulin resis-
tance with a variable insulin deficiency.

**Challenges of Managing Type 2 Diabetes**

Traditional protocols for managing type 2 dia-
betes begin with diet, exercise, and education, then
progress to oral agents (first of 1 class, then of 2, and
perhaps even agents from 3 or 4 classes), before
finally initiating insulin therapy. Treatment within
the context of changing goals, patient noncompli-
cance, and natural disease progression provide the
rationale for progression to insulin.

**Changing Goals**

Just 15 years ago, algorithms in textbooks were
designed with the goal of maintaining glucose levels
below 200 mg/dL. Not until 1997 did the ADA
publish official glucose goals. (See Table 1 for 2003
guidelines.) These goals were based on results from
the Diabetes Control and Complications Trial
(DCCT), a clinical study conducted from 1983 to
1993 involving 1441 volunteers with type 1 diabetes
in 29 medical centers in the United States and
Canada. The United Kingdom Prospective Diabetes
Study (UKPDS), a 20-year trial that recruited 5102
patients with type 2 diabetes from 23 clinical centers
in England, Northern Ireland, and Scotland, con-
firmed the ADA goals. The conclusions drawn from
these studies of patients with type 1 or type 2 dia-
betes were consistent: lowering blood glucose and
glycosylated hemoglobin (HbA1c) levels would
reduce the risk of microvascular complications.

Goals for lowering HbA1c levels have shifted
downward, from below 7% (in the 1997 guidelines,
intervention suggested levels above 8%) to the most
recent goal of less than 6.5% announced by the
American Association of Clinical Endocrinologists
(AACE). These changes are based on data such as
that from the National Health and Nutrition
Examination Survey (NHANES II and III), which
revealed the percentage of patients with diabetic
retinopathy begins to escalate when fasting plasma
sugar (FPG) levels rise to 120 mg/dL and HbA1c
levels are 6.2%. Even patients with impaired glu-
cose tolerance have an increased risk of macrovascu-
lar disease. It is imperative to understand that, in
patients with anything higher than normal glucose
levels, the relative risk of death due to cardiovascular
disease increases 1.5 to 2.5 times.

Given current medications and technology,
these goals may be difficult to attain, and/or are
unrealistic for many patients. Patients with type 1
diabetes in the DCCT study who were assigned to
the intensive therapy group received 3 to 4 daily
insulin injections or treatment with an insulin
pump, and had reduced their HbA1c levels from a
mean value of 9% to a median of 7.2% after 6.5
years, had glycosylated hemoglobin levels that rose
to 7.7%, as was discovered in an observational fol-
low-up study to the DCCT (Epidemiology of
Diabetes Interventions and Complications
[EDIC]). However, tight control was important,
because even though control had declined, sub-
jects in the intensive therapy arm of the
DCCT/EDIC study had a 75% lower risk of pro-
gression of retinopathy ($P<0.001$). Risk of renal dis-
ease, as measured by microalbuminuria, was also
reduced in the group that had undergone inten-
sive (3 to 4 insulin injections per day) versus con-
tventional therapy (1 to 2 injections per day).

**Realities of Achieving Compliance**

Nonpharmacologic Therapies. Proper nutrition

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Table 1. ADA Targets for Glycemic Control

<table>
<thead>
<tr>
<th>Biochemical Index</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial plasma glucose</td>
<td>90–130 mg/dL (5–7.2 mmol/L)</td>
</tr>
<tr>
<td>Peak postprandial plasma glucose</td>
<td>&lt;180 mg/dL (&lt;10 mmol/L)</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>&lt;7 %</td>
</tr>
</tbody>
</table>

and exercise are vital to management of type 2 diabetes, and are the most cost-effective therapies available. These nonpharmacologic interventions can help achieve normalization of blood glucose and lipid levels. In type 2 diabetes, reducing caloric intake and weight, even if ideal body weight is not achieved, can decrease insulin resistance. To be successful, current diet recommendations must take into consideration the individual’s specific tastes and financial means. Detailed information concerning nutritional management of type 2 diabetes may be found in the 2003 Clinical Practice Recommendations published by the ADA (http://care.diabetesjournals.org/cgi/content/full/26/suppl_1/s51). Furthermore, referral to a diabetes educator or a registered dietician is paramount in achieving dietary changes, because such an expert can interpret the intricacies of the diet for the patient and tailor it to his or her specific food preferences and caloric requirements.

Because the major complication of type 2 diabetes is macrovascular disease, it is essential to emphasize to patients that exercise increases insulin sensitivity. Peripheral utilization of glucose increases, not only during the period of exercise itself, but for up to 48 hours afterward.7 By reducing plasma glucose, exercise lowers blood pressure and lipid levels, both of which significantly contribute to cardiovascular morbidity.

The reality of nonpharmacologic therapy is that compliance is poor. Data from NHANES III revealed that 31% of adults with type 2 diabetes engage in no physical activity, and 38% participate in less than the recommended amount of activity; 62% eat less fruit and vegetables than is suggested, and 66% receive more than 30% of their calories from fats. Even more troubling, considering the correlation between obesity and type 2 diabetes, is that NHANES III data reveal that nearly one half (46%) of all patients with type 2 diabetes are obese.10 In light of this stark realization and understanding the natural progression of the disease, clinicians often use pharmacologic management to normalize glucose levels.

"Failure" with Oral Hypoglycemic Agents. Choosing oral agents to attain optimal glycemic control, by supplementing whatever benefits diet and exercise alone may achieve, is a very complex matter. Many factors must be considered: patient weight; blood glucose levels according to self-monitoring and laboratory evaluation; symptoms, level of activity, and comorbid illnesses; and all other medications (Figure 1). Several agents in different pharmacologic classes with different mechanisms of action and target organ sites now permit the clinician to choose monotherapy or the right combination of multiple drug therapy, possibly with insulin, in an effort to allow the patient to approach ideal levels of FPG and HbA1c and avoid microvascular and macrovascular complications (Table 2).

In general, if one oral agent no longer controls the patient's glucose levels, an agent from a different class is added. The rationale for this approach is illustrated by a study conducted by DeFronzo et al, of 921 moderately obese patients with type 2 diabetes in a large, randomized, parallel-group, double-blind investigation. In this study, patients "failing" on glyburide (fasting plasma glucose levels >140 mg/dL) were either continued on glyburide, changed to metformin, or given both agents. Results revealed no change in glucose levels when patients were switched from sulfonylurea therapy to metformin. However, when metformin was added to the sulfonylurea, plasma glucose levels decreased dramatically. The additive impact of metformin and glyburide was more effective than either agent alone (Figure 2).11 This same pattern is seen in virtually all studies comparing 2 different classes of oral agents. Such corroborating data reveal using medications from 2 or 3 different classes with different mechanisms of action may be successful at attaining metabolic control.

Patients with excellent glucose control may occasionally need to discontinue oral agents, thus requiring the move to insulin. Patients who have been
taking metformin may develop decreased renal function. With this newly developed renal disease, metformin must be discontinued to reduce the risk for lactic acidosis. Other patients may achieve glucose control by using thiazolidinediones (rosiglitazone and pioglitazone), medications that often result in significant weight gain or edema. The only way to reverse these complications is to discontinue those drugs.

Even for patients whose compliance is excellent — they attempt to control their diet and their weight, and they take their medications as prescribed — a time may come when this combination fails. It is not necessarily the patient who fails. Misdiagnosis may have occurred at the onset, or this innately progressive disease may have advanced beyond the patient's control.

Misdiagnosis: Type 1 Masquerading as Type 2. Occasionally patients with type 2 diabetes seem to have a need for insulin therapy within months or a few years of diagnosis, earlier than is customary in this population. Clinicians should then consider a diagnosis of latent autoimmune diabetes in adults, a form of type 1 diabetes. These individuals are generally older than 25 years, unlike the classic patient with type 1 disease. In some studies, these patients are thinner than typical patients with type 2 diabetes; in other studies, there is no difference in weight. Laboratory analyses to confirm this diagnosis are islet cell antibodies and antiglutamic acid decarboxylase (GAD) antibodies, both consistent with type 1 (but not type 2) diabetes. The natural progression of this form of diabetes, like other forms, is gradual advancement toward a requirement for insulin.

**Type 2 Diabetes: A Progressive Disease**

The natural history of type 2 diabetes seems to begin with an ever-increasing resistance to insulin 5 to 10 years before elevated glucose levels appear (Figure 3). To compensate for this phenomenon, insulin levels rise, but glucose levels remain normal for approximately 10 years, when β-cell failure occurs, insulin levels decline, and blood glucose rises to progressively higher levels. Because lifestyle changes seem to affect insulin resistance, they are probably most effective before a diagnosis is made. In contrast, oral hypoglycemic agents may be effective at different points along this continuum of illness. For example, the insulin secretagogues, sulfonylureas, and meglitinides are most effective early in the disease because endogenous insulin production can still be stimulated, even though it has diminished. The insulin-sensitizing drugs may be used at any point in the disease process. Metformin, the only biguanide available in the United States, decreases hepatic glu-

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**Table 2. Pharmacologic Classes of Agents to Control Hyperglycemia in Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Class</th>
<th>Action</th>
<th>Contraindications</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones—e.g., rosiglitazone, pioglitazone</td>
<td>Bind to peroxisome proliferator activated receptor-gamma (PPARγ) in muscle, fat, and liver to decrease insulin resistance</td>
<td>Contraindication: Class III/IV heart failure</td>
<td>Caution: Active liver disease/function tests &gt;2.5 x normal</td>
</tr>
<tr>
<td>Insulin secretagogues—e.g., sulfonylureas: glyburide, glipizide, gliclazide; Meglitinides: repaglinide, nateglinide</td>
<td>Stimulate pancreatic β-cells to increase insulin output</td>
<td>Contraindication: Known hypersensitivity to class</td>
<td></td>
</tr>
<tr>
<td>Biguanides—e.g., metformin</td>
<td>Target liver to decrease glucose production</td>
<td>Contraindication: Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance)</td>
<td>Caution: Liver disease, age&gt;80, hypoxic states</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors—e.g., acarbose &amp; miglitol</td>
<td>Inhibit intestinal enzymes that break down carbohydrates, which delays carbohydrate absorption</td>
<td>Contraindication: Cirrhosis, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, or in patients predisposed to intestinal obstruction, chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>Target insulin-sensitive tissue to increase glucose uptake</td>
<td>Contraindication: Known hypersensitivity to class</td>
<td>Caution: Liver disease, age&gt;80, hypoxic states</td>
</tr>
</tbody>
</table>

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**Figure 2. Fasting Plasma Glucose: Mean Change from Baseline**

![Figure 2. Fasting Plasma Glucose: Mean Change from Baseline](image_url)
cose production by improving hepatic insulin action. It also enhances muscle glucose uptake and utilization. The thiazolidinediones enhance muscle tissue sensitivity to insulin; to a lesser degree, they may also suppress hepatic glucose production. Alpha-glucosidase inhibitors act at the small intestine to inhibit the α-glucosidase enzymes, thus slowing the digestion of carbohydrates and delaying the absorption of glucose on the local level. This class of oral agents may also be utilized at any point in the disease process.

No evidence suggests the best protocol to follow for the use of oral agents in the treatment of type 2 diabetes. Furthermore, all of these agents have different target organ sites, be it liver, pancreas, small intestine, or muscle tissue. The weak link in treating patients with oral agents is the stimulation of insulin. According to data from the UKPDS, β-cell failure inevitably occurs regardless of intervention, (Figure 4). Thus, oral medications treating insulin resistance may continue to be useful, but if sufficient insulin is not produced in the pancreas so that insulin sensitizers can work with it, exogenous insulin becomes a requirement.

**MANAGING TYPE 2 DIABETES WITH INSULIN THERAPY**

**CATEGORIES OF INSULIN**

Three major classes of insulin are currently available in the United States. They are classified in terms of their actions as rapid-acting (eg, lispro and regular insulin), intermediate-acting (eg, NPH), and long-acting (eg, insulin glargine). All are synthetic insulin analogues of human insulin. In general, animal preparations are no longer used. Specific types of insulin, along with a general profile of their actions (onsets, peaks, and durations), are listed in Table 3. Generally speaking, rapid-acting insulin is given premeal for postprandial insulin coverage, whereas intermediate- and long-acting insulin may be given in the morning or evening to maintain a basal or more constant effect (Table 3).

The importance of tailoring care to the individual in accordance with his or her self-monitoring of glucose levels cannot be emphasized enough, because each individual’s response to insulin is unique. One patient taking regular insulin may see his or her regular insulin peak in fewer or more hours than another patient. The same patient given the same insulin in the same manner on 2 different days may have his or her insulin level peak differently on each day.

**REGULATING INSULIN DOSAGES**

Glucose patterns are fairly stable in nondiabetic persons throughout the day. They have a low basal

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**Figure 3. Natural History of Type 2 Diabetes**

- Thiazolidinedione - Biguanide
  - **Lifestyle**
  - **SU**
  - **Insulin**

- **Glucose (mg/dL)**
  - Fasting Glucose
  - Postmeal Glucose

- **Relative Function (%)**
  - Insulin Resistance

**Figure 4. Conventional Therapies Do Not Influence β-Cell Failure: UKPDS**

- **Overweight**
  - Conventional Chlorpropamide, Metformin, Glibenclamide

- **Non-Overweight**
  - β-cell function (%)

**Table 3. Insulins Available in the United States**

<table>
<thead>
<tr>
<th>Types and Preparations</th>
<th>Action Profile (h)</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro/Aspart</td>
<td>0.25--0.5</td>
<td>0.5--1.5</td>
</tr>
<tr>
<td>Regular</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>5--6</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>1--2</td>
<td>6--12</td>
</tr>
<tr>
<td>Lente</td>
<td>1--3</td>
<td>6--15</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultralente</td>
<td>4--6</td>
<td>8--30</td>
</tr>
<tr>
<td>Glargine</td>
<td>8</td>
<td>24</td>
</tr>
</tbody>
</table>
insulin level, with increased but small peaks after each meal. Traditional insulin regimens combine regular insulin and NPH, splitting the dose between morning and evening. With split dosing, insulin peaks do not necessarily occur after each meal (Figure 5). To more closely match what occurs naturally, investigators in the intensive-therapy arm of the DCCT study gave individuals with type 1 diabetes regular insulin with each meal and long-acting insulin in the evening. Although a good regimen for individuals with type 1 diabetes, this schedule, like split dosing, is not necessarily ideal for type 2 diabetes. Because of their insulin resistance, patients with type 2 diabetes may require large doses of regular insulin, which then have a delayed onset and a more prolonged mode of action. This may precipitate hypoglycemic events when insulin peaks long after the postprandial hyperglycemic peak. NPH, lente, and ultralente may add to the problem when they are prescribed to provide a basal insulin level because they vary widely in their duration of action, conferring a risk for unpredictable hypoglycemia. The newer synthetic insulins behave in a more predictable manner.

**NEW SYNTHETIC INSULINS**

Insulin lispro and insulin aspart are short-acting insulins, with a rapid onset of action. Insulin levels peak and fall rapidly in patients who take them before a meal. These drugs are therefore effective for meal coverage but require a baseline insulin as a supplement. Glargine, a long-acting synthetic insulin that provides a steady level of insulin similar to that by an insulin pump, may work well in conjunction with lispro or aspart (Figure 6). In a study by Lepore et al comparing NPH, ultralente, and glargine, glargine provided the steadiest and most predictable insulin levels over a 24-hour period. As expected, glucose levels remained best controlled with glargine compared with NPH and ultralente. These levels were surpassed only by those attained when patients used an insulin pump that delivers a continuous subcutaneous infusion of insulin.

**EVIDENCE-BASED INSULIN THERAPY IN TYPE 2 DIABETES**

Studies have been conducted on the use of insulin in type 2 diabetes, usually in conjunction with oral hypoglycemic agents, in an attempt to answer the question of whether the new synthetic insulins offer the ideal regimen for type 2 diabetes. In 1992 Yki-Jarvinen et al compared 153 patients in 4 treatment groups plus a control group. Control subjects received oral agents alone; none took insulin. The 4 insulin-treated groups were as follows: (1) morning NPH and various oral agents; (2) evening NPH and oral agents; (3) 70/30 NPH mixed with regular insulin administered twice daily; and (4) evening NPH with injections of regular insulin before meals. All 4 insulin-treated groups improved significantly more than controls (0.5% ± 0.2%; P < .001), with similar decreases in the mean values of glycated hemoglobin. The main noteworthy difference was that those taking an evening dose of NPH gained less weight than participants in the other groups (1.2 kg ± 0.5 kg).

A later study by Yki-Jarvinen et al attempted to investigate whether this finding could be reproduced in another population. In a randomized controlled trial of 96 patients who were poorly controlled on sulfonylureas (HbA1C 9.9%), 4 regimens were administered: (1) intermediate-acting insulin at bedtime with glyburide and placebo; (2) intermediate-
acting insulin at bedtime with metformin and placebo; (3) intermediate-acting insulin at bedtime with glyburide and metformin; or (4) intermediate-acting insulin at bedtime and in the morning. After 1 year, the patients who had taken bedtime insulin plus metformin had no significant weight change (0.9 kg ± 1.2 kg; P < 0.001) compared with the 2 other groups taking bedtime insulin with other oral agents (3.9 kg ± 0.7 kg, and 3.6 kg ± 0.1.2 kg) or the group receiving twice-daily dosing with insulin alone (4.6 kg ± 1.0 kg). Furthermore, the group on bedtime insulin and metformin experienced superior glycemic control with fewer episodes of hypoglycemia: glycemic control was measured via decreases in HbA1c from 9.7% (± 0.4%) to 7.2% (± 0.2%), a decrease of 2.5% (± 0.4%; P < 0.001).

To further determine the effects of metformin on individuals with type 2 diabetes, Aviles-Santa et al conducted a study in 1999 to investigate how obese patients who were poorly controlled on insulin might fare with the addition of this biguanide. In this study, 43 patients were randomized to receive insulin plus placebo or insulin plus metformin for 24 weeks. Investigators found that the addition of metformin resulted in a 10% reduction in glycosylated hemoglobin levels (6.5% therapeutic versus 7.6% placebo) with less weight gain (0.5 kg gain therapeutic vs 3.2 kg gain placebo) and lower insulin requirements. Increases in insulin dose for the placebo group averaged 22.8 units — 29% more than for the metformin group.

More recent investigations have focused on comparing other agents to insulin and metformin or to insulin alone. One study compared the use of repaglinide in combination with bedtime NPH insulin versus the use of metformin in combination with bedtime NPH insulin. In this trial involving 80 patients over 13 weeks, repaglinide did not fare as well as metformin; fasting blood sugars and weight gain were both less in the metformin/insulin group than in the repaglinide/insulin group. Neither group performed well; glycemic control improved nonsignificantly from 8.4% to 8.1% (P = 0.09) in users of metformin, and deteriorated by 0.4% those using repaglinide (mean changes were from 8.1% to 8.6%; P = 0.03; P = 0.005 between groups).

A second study compared the use of troglitazone versus metformin or insulin monotherapy. Strowig et al randomized 88 diabetic patients to 3 groups for 4 months. Some patients were placed on insulin alone; some on insulin plus metformin; some on insulin plus troglitazone. In all groups, the treatment was successfully titrated to achieve HbA1c levels at or below 7%. The insulin doses required to achieve HbA1c levels <7% ranged from about 70 U to 140 U per day. Subjects taking troglitazone with insulin had the lowest insulin doses. Weight gain was limited in the insulin plus metformin group. Although troglitazone was removed from the US market due to rare cases of hepatocellular injury, similar medications are still available.

In 2001, Yki-Jarvinen summarized the clinical evidence by examining the results of 34 studies conducted between 1966 and 2000 that investigated the use of insulin alone as compared with its use with oral hypoglycemic agents in patients with type 2 diabetes, with specific attention to the effects of these medications on glycemic control, insulin requirements, hypoglycemia, and weight gain. Most of the studies were flawed in that they were relatively short term, failed to titrate insulin to an appropriate goal, or did not adjust medications based on glucose levels throughout the day. The overall conclusion Yki-Jarvinen drew from these analyses was that oral agents are effective adjuncts to insulin therapy. No specific insulin regimen has been shown to be superior in controlling glucose. The only significant difference in the insulin regimens was that with equal glucose control, there was less hypoglycemia with insulin glargine. Metformin as an oral medication and insulin glargine therefore appear to offer the best glycemic control with the least weight gain and the least variation in insulin levels throughout the day.

**The Move to Insulin**

**Barriers to Starting Insulin**

Once it has been determined that a patient requires insulin, multiple barriers may need to be overcome. Some patients perceive the need to begin insulin therapy as a failure on their part, or even as a threat issued by the clinician to get them to increase compliance with diet and oral therapy. They should be informed that lifestyle modifications and oral agents may no longer be adequate because diabetes is a progressive illness, and in their case, insulin is required to avoid complications. Other patients may fear that needing insulin means their illness is severe and they are now guaranteed serious complications or even imminent death. It is important to allay these fears and misconceptions. As with all aspects of this disease, intensive patient education is necessary to assure maximum compliance and optimal glycemic control, and to avoid both short-term complications (hypoglycemia) and long-term complications (microvascular and macrovascular effects).

**Teaching Patients About Insulin Administration**

Patients need to be aware of the type of insulin
(rapid- or longer-acting) and the source of insulin (human or animal) being prescribed because any variation may precipitate hypoglycemia or inadequate control. Some types of insulin are available without a prescription, and all types may be stored at room temperature if the vial is in use. An open bottle of insulin, especially if left at room temperature for more than 30 days, may lose its potency. Thus, all vials being stored for future use should be kept refrigerated. Until recently, patients could be told that rapid- and short-acting insulin will appear clear, while intermediate-acting and long-acting insulins are uniformly cloudy. With the introduction of “clear” long-acting glargine, this simple way of distinguishing short-acting from long-acting insulin is no longer reliable. No visible clumps or precipitates should appear in any insulin.

Although mixtures of short- or rapid-acting and longer-acting insulin are commercially available, patients are generally discouraged from mixing 2 types of insulin in 1 syringe because of the high incidence of errors, especially among individuals whose vision may be impaired. If mixing is to be done, patients must be made aware that they should draw up the short-acting insulin first; if they do otherwise, the long-acting insulin contaminates the short-acting insulin in its bottle. Certain types of insulin, such as regular and lente, cannot be mixed together, and glargine cannot be mixed with any other insulin because of its pH.

When injecting insulin, the patient should administer it subcutaneously, and sites should be rotated between the abdomen, upper arms, thighs, and buttocks to avoid lipohypertrophy. The abdomen absorbs regular insulin faster than any other site, and patients should be cautioned that the change from one injection site to another might affect rate of absorption and thus blood glucose response. Exercise, too, may increase the rate of insulin absorption. Home monitoring of glucose is the best way to regulate insulin properly. It should be carefully taught to patients along with proper injection techniques, insulin storage, and needle disposal.

<table>
<thead>
<tr>
<th>Table 4. Starting Insulin: Basal Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start with 10 U/day bedtime basal insulin dose and adjust weekly.</td>
</tr>
<tr>
<td>FPG Range to Determine Change</td>
</tr>
<tr>
<td>Basal Insulin Dosage</td>
</tr>
<tr>
<td>100-120 mg/dL</td>
</tr>
<tr>
<td>120-140 mg/dL</td>
</tr>
<tr>
<td>140-180 mg/dL</td>
</tr>
<tr>
<td>≥ 180 mg/dL</td>
</tr>
<tr>
<td>Treat to target fasting plasma glucose (FPG), 100-120 mg/dL.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5. When to Go to &gt;1 Injection Per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &gt;7%</td>
</tr>
<tr>
<td>Glucose in AM at goal</td>
</tr>
<tr>
<td>Glucose before dinner &gt;140 mg/dL</td>
</tr>
<tr>
<td>Options</td>
</tr>
<tr>
<td>Add premeal lispro/aspart</td>
</tr>
<tr>
<td>Change to bid premixed insulin: 70/30, 75/25</td>
</tr>
<tr>
<td>Questions</td>
</tr>
<tr>
<td>Discontinue sulfonylurea? (unknown)</td>
</tr>
<tr>
<td>Continue metformin (probably)</td>
</tr>
<tr>
<td>Thiazolidinedione? (unknown)</td>
</tr>
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</table>
by the long-acting insulin, but do not produce enough insulin after their meals. Depending on physician and patient preferences and capabilities, such patients either have premeal lispro/aspart added, or they are changed to a regimen of premixed insulin twice per day. Adjustments of the insulin doses are made based on the insulin pharmacodynamics described earlier (Tables 3 and 4). Sulfonylureas should be discontinued in this scenario while metformin and possibly thiazolidinediones are continued.

**CONCLUSION**

Perhaps most vital to management of type 2 diabetes is understanding that the disease is very heterogeneous. Its complex underlying pathophysiology includes insulin resistance and decreased insulin secretion. Furthermore, each patient is different and may be at different stages of the illness. The treatment of type 2 diabetes seems to be dynamic — changing according to advances in our understanding of the pathophysiology of this disease, the development of more effective pharmaceutical agents, and the evolution of the disease within each patient. Although we understand more and more about these issues, several major questions remain. Perhaps future research and greater clinical experience with this complex and increasingly common illness will hold the key to unlocking these mysteries.

**REFERENCES**


