Insulin Analogs or Premixed Insulin Analogs in Combination With Oral Agents for Treatment of Type 2 Diabetes

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Disclosure: Philip Levy, MD, FACE, has disclosed that he has received grant/research support from Amylin Pharmaceuticals, Inc, MannKind Corp, Novo Nordisk A/S, Pfizer, and sanofi-aventis; and that he is on the speakers bureau for Abbott, Amylin Pharmaceuticals, Inc, Eli Lilly and Company, GlaxoSmithKline, Merck, Novartis Pharmaceuticals, Novo Nordisk A/S, Pfizer, and sanofi-aventis.

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Abstract

Context

Type 2 diabetes is a progressive disease that is reaching epidemic proportions. Whereas most patients are initially managed with oral antidiabetic agents (OADs), the majority eventually require insulin to maintain glycemic control. The availability of insulin analogs (rapid-acting, long-acting, and premixed), with more predictable time-action profiles than human insulin preparations and simple-to-use insulin delivery devices, can help ease the transition to insulin therapy, which is often delayed until glycemic control has been inadequate for several years.

Objective

To review the rationale for and strategies to initiate therapy with insulin analogs earlier in the course of type 2 diabetes. Practical barriers that must be overcome to successfully initiate insulin therapy in patients with type 2 diabetes are also briefly described.

Design

Narrative review of clinical evidence and current diabetes treatment guidelines.

Setting and Patients

Outpatients with type 2 diabetes inadequately managed with OADs alone.

Interventions

Three of the most common approaches to initiating insulin therapy with analogs are considered, with clinical evidence and detailed dosing algorithms provided. These approaches include: (1) addition of a basal insulin analog to oral therapy to reduce and stabilize fasting plasma glucose, (2) supplementation of oral therapy with a rapid-acting mealtime insulin analog to control postprandial glucose excursions, and (3) addition of or switching to a premixed insulin analog, which can be used to control both fasting and postprandial glucose in 1 injection.

Conclusions

Selection of appropriate insulin analog regimens and individualization of therapy can help patients achieve recommended glycemic goals while minimizing hypoglycemia. Education about the eventual need for insulin and improvements in insulin preparations and delivery systems at the time of diagnosis can also help overcome patient barriers.

Introduction
In 2005, 20.8 million adults in the United States were estimated to have diabetes mellitus.[1] This number is expected to increase to 29 million by 2050.[2] Most cases of diabetes (90% to 95%) are type 2,[3] which has been increasing in prevalence everywhere in the United States in parallel with the obesity epidemic. All ages, ethnic groups, education levels, and both sexes are susceptible.[4]

Several long-term randomized trials of diabetes care and outcomes demonstrated that achieving near-normal glycemia, in terms of fasting and postprandial plasma glucose and glycosylated hemoglobin (A1C) levels, is crucial for avoiding or delaying long-term microvascular complications such as retinopathy, nephropathy, and neuropathy.[5–7] The evidence that intensive therapy also delays macrovascular disease is less compelling. However, after more than 17 years of follow-up in one of these trials, intensive insulin therapy that targeted normoglycemia was shown to reduce the risk of cardiovascular disease by 42%. Compared to conventional therapy (defined as 1-2 injections of insulin daily with no glycemic goals other than to prevent symptoms of hyperglycemia and hypoglycemia), the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease was 57% lower with intensive therapy.[8]

Maintenance of tight glycemic control in patients with type 2 diabetes requires timely adjustments and changes in therapy when goals are not met. While the majority are initially treated with oral antidiabetic drugs (OADs),[9] most patients ultimately require insulin therapy to maintain glycemic control.[10] Commonly used OADs and some newer therapies have limited potential to lower A1C, by just 0.5 to 1.5%. Insulin, when used in appropriate doses, can decrease any level of A1C to near goal, limited only by its potential to cause hypoglycemia.[11] The aim of this article, therefore, is to provide evidence-based practical guidance for improving glycemic control in patients with type 2 diabetes. The emphasis is placed on how insulin therapy, in particular, with insulin analogs and premixed insulin analogs, can be initiated in patients who currently are inadequately managed with OADs alone.

**Glycemic Targets**

Currently accepted treatment targets for A1C levels, according to the American Diabetes Association (ADA), are less than 7.0% or as close to normal as possible without causing undue hypoglycemia.[12] The American Association of Clinical Endocrinologists (AACE) recommends a target of 6.5% or less.[13] However, in a study reporting glycemic control rates among US adults with type 2 diabetes from 1999 to 2000,[14] less than 36% of patients reached a goal of less than 7%.

The ADA and AACE recommendations also differ slightly for optimal control fasting plasma glucose (FPG) and postprandial glucose (PPG) (Table 1). Although both are strongly correlated with A1C,[15] PPG may more accurately predict overall glycemic control and correlate better with A1C than FPG.[16] The relative contribution of PPG to A1C increases as glycemic control improves while the relative contribution of FPG increases gradually with rising A1C.[17]

**Progression of Therapy in Patients With Type 2 Diabetes**

Type 2 diabetes management has traditionally followed a stepwise approach, beginning first with diet and exercise, then adding 1 or more OADs when dietary modifications and exercise are inadequate.[18] Algorithms for the management of diabetes have been developed by AACE/American College of Endocrinology (ACE)[18] and ADA/European Association for the Study of Diabetes (EASD).[11] Both stress tight glycemic control, rapid addition of medications or transition to new regimens when goals are not met, and early insulin therapy, particularly when A1C levels are greater than 8.5% or severe hyperglycemia (FPG >250 mg/dL) is present.[11,18]

Because the pathophysiology of type 2 diabetes involves both insulin resistance and progressive failure of beta-cells to secrete insulin, various OADs have been developed to increase insulin secretion (insulin secretagogues) and insulin sensitivity (insulin sensitizers) (Table 2).[19] The alpha-glucosidase inhibitors (AGIs) are another class of agents that act by delaying intestinal carbohydrate absorption, but have limited A1C-lowering capacity (0.5% to 0.8%).[11]

The recent consensus recommendation from the ADA/EASD is to begin metformin as the initial step in type 2 diabetes management, along with diet and exercise.[11] Before this more aggressive approach,
pharmacotherapy was often initiated with an insulin sensitizer (metformin or a thiazolidinedione) or an oral secretagogue (a meglitinide or sulfonylurea).[20] Monotherapy usually results in initial treatment success followed by a slow, but steady, rise in A1C.[10,21–23] A recent study of patients receiving oral monotherapies including metformin, rosiglitazone, or glyburide reported that 60%, 64%, and 76%, respectively, had A1Cs of 7% or higher after the fourth year of follow-up.[24] Combination oral therapy with a secretagogue and sensitizer is typically the next step,[18] although some patients, such as those whose blood glucose greatly exceeds treatment goals, may actually begin treatment using combination OAD therapy.[25] Several newer therapies, both injectable and oral, are now available and may be added (Table 2; discussed subsequently).

Although initiation of insulin therapy was typically uncommon in type 2 diabetes management until after oral agents failed,[26–29] the paradigm for diabetes management has been shifting. Because beta-cell failure is progressive, most patients with type 2 diabetes will ultimately require insulin therapy to achieve glycemic goals, and thus insulin should no longer be considered a last resort because of failure or fault of the patient. Rather, there is an emerging awareness that using insulin earlier in the course of disease is physiologically sound and an integral part of adequate disease management.[29–31] Delays in starting patients with type 2 diabetes on insulin may be due to patient resistance or physician uncertainty about how to make this transition.[32] Reluctance to initiate more aggressive therapy, particularly insulin, or concern about hypoglycemia, may explain why ideal glycemic control still has not been achieved.[33]

**Insulin Formulations: Human Insulins vs Insulin Analogs**

The aim of insulin administration in patients with diabetes is to mimic normal physiologic secretion of insulin to control both FPG and PPG.[34] Human insulin formulations have been used extensively for the treatment of type 1 or 2 diabetes, but their utility for achievement of tight glycemic control is limited; that is, their pharmacokinetic/pharmacodynamic profiles do not mimic the physiologic profile of insulin secretion found in individuals without diabetes. Regular human insulin (RHI), for example, is used to control PPG, but it is slowly absorbed, necessitating dosing 30-45 minutes before meals. RHI is also cleared slowly from the circulation, which increases risk of hypoglycemia between meals. For basal insulin replacement, the intermediate-acting neutral protamine Hagedorn (NPH) is often used. NPH is a human insulin that has a distinct peak in action that increases the risk of hypoglycemia. Two or more injections of NPH are required for adequate basal 24-hour coverage. In addition, both RHI and NPH exhibit considerable variability in absorption. This variability is apparent between patients, but more importantly, variation also occurs within the same individual.[35–37] This variation means that, when giving identical doses of subcutaneous insulin injections – even at the same dose, site of injection, time of day, with controlled dietary intake and physical activity – different and unpredictable glycemic effects can result.[37] The time-action profiles of human insulin formulations can therefore result in insulin effects that do not match the glucose demand or the patient’s needs.[38]

New insulin analogs and premixed insulin analogs have overcome some limitations of human insulins. Three rapid-acting analogs (insulin lispro, aspart, and glulisine), 2 long-acting insulin analogs (insulin glargine and insulin detemir), and 3 premixed insulin analogs (biphasic insulin aspart 70/30, insulin lispro 75/25, and insulin lispro 50/50) are currently available in the United States (Table 3).[39]

Compared with RHI, rapid-acting insulin analogs show faster absorption, more rapid onset of activity, and a shorter duration of action.[39,40] These pharmacokinetic and pharmacodynamic improvements result in superior PPG control and decreased risk of hypoglycemia. In contrast to RHI, which must be administered at least 30 minutes before a meal, rapid-acting insulin analogs can be administered within 15 minutes before eating or even after a meal, thereby synchronizing insulin administration with food absorption and the associated increase in blood glucose.[41,42] They are also more convenient for patients with unpredictable meal times.

Long-acting insulin analogs are designed to provide up to 24-hour basal insulin levels with once- or twice-daily administration. Compared with previous intermediate- or long-acting human insulins, long-acting insulin analogs have relatively flat time-action profiles, and they also decrease the risk of
Approaches to Insulin Initiation in Type 2 Diabetes: Lessons From Clinical Trials

Three approaches for initiation of insulin therapy have been widely used: (1) addition of basal insulin to OADs,[32] (2) addition of a premixed insulin to OADs,[43,44] or (3) addition of mealtime insulin to ongoing treatment with 1 or more oral agents. Each of these approaches has been investigated using insulin analogs as compared to human insulin formulations. In clinical practice, treatment should be individualized to meet patients' needs. In some cases, a complete transition to insulin without continuing oral medication provides effective control and is appropriate.

Basal Insulin Analogs and Oral Antidiabetic Drugs

Studies show that addition of a long-acting insulin analog to oral therapy (secretagogues and sensitizers) is effective for improving glycemic control in patients with type 2 diabetes. The Treat-to-Target Study[23] compared adding glargine or NPH insulin once daily to ongoing treatment with 1 or 2 oral drugs in 756 overweight individuals and an A1C greater than 7.5%. Insulin was titrated using a simple algorithm aimed at achieving a target FPG ≤ 100 mg/dL. After 24 weeks of treatment, FPG declined from 198 to 117 mg/dL for patients who received insulin glargine and from 194 to 120 mg/dL for those who received NPH insulin. The respective declines in A1C were from 8.61% to 6.96% and from 8.56% to 6.97%. The major difference between regimens was that nearly 25% more patients using insulin glargine achieved these improvements without documented nocturnal hypoglycemia (33.2% vs 26.7%). The rate of symptomatic hypoglycemia was also lower with insulin glargine.[23]

In the 9-month Lantus plus Metformin (LANMET) study[45] of 110 patients, an A1C of approximately 7.15% was reached with either insulin glargine or NPH. The incidence of symptomatic hypoglycemia was lower with glargine (4.1 vs 9.0 episodes per patient-year; \( P < .05 \)) during the first 12 weeks but not significantly different during the remaining 6 months of therapy.[45] In the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) study[46] with 7893 adults, glargine dosed with an active titration schedule (monitored each week by physician) showed significantly greater A1C reduction (1.5% vs 1.3%, \( P < .0001 \)) than glargine dosed with a usual titration schedule (monitored every 6 weeks by physician with no unsolicited contact between visits).[46] A meta-analysis of results from several 24- to 28-week studies that included 1142 patients also indicated that once-daily insulin glargine was as effective as NPH insulin in achievement of A1C ≤ 7%, but with significantly decreased risk for hypoglycemia (54.2% vs 61.2%; \( P = .0006 \).[47]

Insulin detemir has also been used effectively as basal therapy in type 2 diabetes. In a 26-week study, addition of insulin detemir to oral therapy decreased A1C similarly by 1.8% to 6.8% vs 1.9% to 6.6% for NPH insulin, while insulin detemir was associated with significantly less weight gain (1.2 vs 2.8 kg; \( P < .001 \).[48] A 47% reduction in the risk of all hypoglycemia was also seen with insulin detemir compared with NPH (\( P < .001 \)), while the risk for nocturnal hypoglycemia was reduced by 55% with insulin detemir compared with NPH.[48] Treatment with insulin detemir has consistently been shown to result in less weight gain compared with NPH insulin.[48–50] In 1 study, patients treated with insulin glargine also gained less weight (0.4 kg) than those treated with NPH insulin (1.4 kg; \( P = .0007 \)), although trials with insulin glargine have not reported weight benefits as consistently as those with insulin detemir.[51,52] Preliminary results from another trial also suggest that insulin detemir in combination with OADs may be associated with less weight gain than insulin glargine and OADs.[53]

Premixed Insulin Analogs

Premixed insulin analogs permit delivery of both basal and prandial insulin in a single injection at mealtimes. Three premixed insulin analog formulations are currently available in the United States: insulin lispro 75/25, which contains 75% insulin lispro protamine suspension and 25% insulin lispro; insulin lispro 50/50, which contains equal proportions of the same; and biphasic insulin aspart 70/30 (BIAsp 70/30), which contains 70% insulin aspart protamine suspension and 30% insulin aspart. These formulations are more convenient compared with basal-bolus therapy (ie, fewer injections and less monitoring) or with older premixed human insulin formulations that contained NPH and RHI as the
basal and prandial components, respectively. The rapid-acting component of premixed insulin analogs is absorbed and cleared more quickly, thereby allowing mealtime administration and providing better prandial glycemic control, as well as potentially lower risk for hypoglycemia. The protaminated portion of the analogs impart a longer duration of action.[43,54]

The ease of transitioning patients to insulin therapy with premixed insulin analogs is illustrated by the 1-2-3 Study,[44] an observational trial that included 100 patients not achieving control on OAD therapy with or without basal insulin. The trial evaluated whether addition and self-titration of biphasic insulin aspart 70/30 (BIAsp 30) could achieve AACE or ADA targets for A1C (≤ 6.5% and < 7.0%, respectively). Patients continued oral agents, but stopped basal insulin and added 1 injection of BIAsp 30 (12 units or 70%-100% of the prior basal insulin dose) within 15 minutes of supper initiation. Patients self-titrated their BIAsp 30 dose with investigator guidance every 3 or 4 days to achieve a pre-breakfast FPG of 80-110 mg/dL. At 16 weeks, a pre-breakfast injection of 6 units of BIAsp 30 was added if week 15 A1C was > 6.5% and secretagogues were discontinued. After an additional 16 weeks, 3 units of pre-lunch BIAsp 30 was added if A1C was still above this goal. Addition of once-daily BIAsp 30 before supper enabled 21% of the patients to achieve A1C ≤ 6.5% and 41% to achieve A1C < 7.0%. The respective values with 2 daily injections of BIAsp 30 were 52% and 70%, and those with 3 injections were 60% and 77% (Figure 1).[44]

Addition of a Rapid-Acting Insulin Analog at Mealtimes

Designed for delivery at mealtimes to control PPG excursions, rapid-acting insulin analogs (aspart, glulisine, or lispro) can be added to a basal or premixed insulin regimen or, in some patients, used separately without basal coverage. For patients using basal insulin, one strategy is to add a rapid-acting analog to the largest meal and then cover additional meals as needed. For patients using a premixed insulin regimen at breakfast and supper, a rapid-acting insulin analog can be added to provide lunch coverage when needed. Rapid-acting analogs can be dosed within 15 minutes of starting a meal and provide better postprandial control compared to RHI.[39] The more rapid pharmacodynamic effects of rapid-acting analogs also decrease the risk of post-absorptive (between-meal) hypoglycemia compared to RHI.[40]

Comparison of Basal and Premixed Regimens

For patients who may prefer a simpler insulin regimen, premixed insulin analogs offer a solution without compromising glycemic control. The need for fewer daily injections may be easier to accept, especially when first transitioning to injections; acceptance of therapy and adherence should improve, also shown to improve A1C levels.[55] Results from several large-scale clinical trials have indicated that the use of a premixed insulin analog twice daily (BID) is superior to insulin glargine daily (QD) for lowering A1C in patients with type 2 diabetes. There may be several reasons for this. In a randomized, crossover study in 12 subjects in which the glucose level was held constant using a euglycemic clamp technique, the glucose-lowering effect of BIAsp 70/30 given BID was 34% greater than with QD insulin glargine. Additionally, the insulin area under the curve (AUC) was 28% higher, and endogenous insulin secretion was suppressed to a greater degree with BIAsp 70/30 (potentially sparing beta-cells) compared with insulin glargine QD.[56]

The Initiation of Insulin to Reach A1C Target (INITIATE) study was a 28-week parallel-group trial of 233 insulin-naive patients with an A1C ≥ 8.0% on > 1000 mg/day metformin alone or in combination with other OADs.[57] Metformin was adjusted up to 2550 mg/day and patients using thiazolidinediones continued on or switched to pioglitazone. Secretagogues were discontinued in both groups. Insulin therapy was started with either 5-6 units BIAsp 30 BID or 10-12 units insulin glargine at bedtime. Treatment was targeted to achieve an FPG of 80-110 mg/dL. At the end of 28 weeks, A1C was 6.91% for the BIAsp 30 group vs 7.41% for those treated with insulin glargine. In addition, more BIAsp 30-treated patients reached the A1C targets of ≤ 6.5% (42% vs 28%) and < 7.0% (66% vs 40%) than those who received insulin glargine. Patients who received BIAsp 30 experienced 3.4 episodes of minor hypoglycemia per patient-year vs 0.7 for insulin glargine. Weight gain with BIAsp 30 (5.4 kg) was also higher than that observed for patients who received insulin glargine (3.5 kg).[57] In a similar study in
which secretagogues were continued in patients remaining on insulin glargine, the decrease in A1C was 0.5% lower with BIAsp 30 plus metformin compared with glargine plus glimepiride.\[58\] In a recent study, more than 75% of patients who were inadequately controlled on optimal doses of metformin and pioglitazone reached an A1C < 7% after BIAsp 30 BID was added.\[59\] Finally, a regimen using BIASP 30 BID in 715 insulin-naive type 2 diabetes patients was as effective in lowering A1C as a basal-bolus regimen of insulin detemir-insulin aspart (1.42% vs 1.69%, \textit{P} = .106) while resulting in fewer major hypoglycemic events.\[60\]

Malone and colleagues compared 75% insulin lispro protamine suspension and 25% insulin lispro (lispro 75/25) BID plus metformin vs insulin glargine QD plus metformin in 105 patients who were starting insulin treatment. The premixed insulin analog resulted in a significantly lower A1C than insulin glargine (7.4% vs 7.8%) and a higher percentage of patients who achieved A1C ≤ 7.0% (42% vs 18%). However, weight gain was significantly higher (2.3 vs 1.6 kg), and hypoglycemia occurred significantly more often (0.68 vs 0.39 episodes/patient per 30 days) with lispro 75/25.\[61\] In a second study of 97 patients inadequately controlled with insulin alone or insulin plus oral drugs, reductions from baseline in A1C were significantly greater with metformin plus lispro 75/25 vs metformin plus glargine (1.0% and 0.42%, respectively; \textit{P} < .0001).\[62\]

The greater A1C lowering obtained with premixed insulin analogs compared with insulin glargine in clinical trials has also been documented in clinical practice. Based on a retrospective analysis of electronic medical records from 2.4 million patients in the United States, including 8166 insulin-naive individuals, patients using a premixed insulin analog BID had a 0.49% to 0.65% greater decrease in A1C compared to those using insulin glargine QD or human insulin 70/30 BID.\[63\]

These results obtained with premixed insulin analogs vs basal long-acting insulin analogs contrast sharply with those from a study of insulin glargine plus OADs vs premixed human insulin 70/30 alone.\[64\] In this 24-week study, 371 insulin-naive patients with A1C 7.5% to 10% while on OADs (sulfonylurea plus metformin) were randomly assigned to QD morning insulin glargine plus glimepiride and metformin or premixed human insulin 70/30 BID with discontinuation of the OADs. Insulin dosages were titrated to achieve FPG ≤ 100 mg/dL. Patients who received insulin glargine and OADs had a significantly greater decrease from baseline in A1C (-1.64%) vs those treated with premixed human insulin alone (-1.31%). In addition, the rate of nocturnal hypoglycemia was significantly lower with insulin glargine and metformin vs the conventional premixed insulins alone (28.6% vs 45.5%).\[64\]

**Newer Therapies for Diabetes Management**

Newer agents with novel mechanisms of action are available or in development. Exenatide, for example, is a subcutaneously injected incretin mimetic that enhances glucose-dependent insulin secretion. Recent clinical trial results have indicated that exenatide administration near mealtimes can reduce PPG.\[65\] In published trials, the reduction in A1C observed in patients treated with exenatide is modest, approximately 1%. One distinct benefit with exenatide, however, is its effect on body weight, with patients reporting weight reductions of 1.6-2.8 kg over 30 weeks.\[66\] Dipeptidyl peptidase-IV (DPP-IV) is an enzyme that inactivates incretins (ie, glucose-dependent insulino tropic polypeptide [GIP] and glucagon-like peptide-1 [GLP-1]) that have antidiabetic actions.\[67\] Blockade of this enzyme with oral DPP-IV inhibitors is another therapeutic strategy.\[68\] The first DPP-IV inhibitor, sitagliptin, has recently been approved in the United States for treatment of patients with type 2 diabetes. Addition of another DPP-IV inhibitor, vildagliptin, to metformin decreased A1C by 0.5% to 1.1% without weight gain.\[69\] A recent review gives more comprehensive information on these emerging therapies.\[70\] Due to their lower overall glucose-lowering activity, limited clinical data, and relative expense, these agents were not included in the recently published ADA/EASD algorithm.\[11\]

Inhaled RHI is also now available. When compared with subcutaneous RHI, inhaled insulin has a more rapid onset of action. However, the length of time that inhaled insulin and RHI persist in the circulation are similar.\[71\] In combination with basal insulin, inhaled insulin has shown comparable efficacy and safety to standard therapy with NPH and RHI injected subcutaneously.\[71\] Head-to-head trials with insulin analogs have not yet been performed.
How to Initiate, Integrate, Titrate, and Select Insulin Therapy

The clinical evidence described previously supports the view that ADA and AACE targets for patients with type 2 diabetes who are failing oral therapy can be achieved with basal or premixed insulin analogs plus OADs (see subsequent discussion). This approach to insulin therapy is easy to initiate, adjust, and intensify,[72] and consistent with the ACE/AACE road map to achieve glycemic control (A1C ≤ 6.5%). The road map recommends the following steps in patients who have not achieved A1C goal on a single oral drug: combination therapy with oral agents, addition of an incretin mimetic (eg, exenatide), or addition of basal or premixed insulin to oral treatment. Patients not achieving A1C goal on combination treatment should have basal insulin added if FPG is elevated, bolus insulin added if PPG is elevated, and premixed insulin or basal-bolus insulin therapy if both FPG and PPG are above targets.[18]

Many who start insulin therapy may remain on one or more oral drugs for some time. Metformin and/or a thiazolidinedione are most suitable for combining with premixed insulin analogs or with rapid-acting insulin analogs. Oral insulin secretagogues are not synergistic with rapid-acting insulin[11]; however, a secretagogue can be continued if using a basal insulin analog. Exenatide is not indicated for use in combination with insulin at this time.

Basal-bolus therapy with multiple daily injections (MDI) or an insulin pump is generally considered to be the most physiologic approach to insulin therapy.[43,54] With MDI therapy, basal insulin is injected once or twice per day and short- or rapid-acting prandial insulin is administered with each meal. This approach has been shown to be highly effective for the achievement of tight control over both FPG and PPG, and is now generally viewed as the optimal regimen for insulin therapy for patients with diabetes. [50,73] While highly effective and generally well tolerated, this approach may not be suitable for many patients.[43] MDI therapy requires 4 or more injections per day, along with associated blood glucose measurements and comprehensive education including carbohydrate counting. This approach also involves considerable teaching time for healthcare providers.

Individualized blood glucose targets should be established for each patient and should be aimed at decreasing the risk for hypoglycemia while maintaining good glycemic control. The starting regimen is determined primarily by the degree of hyperglycemia and the current A1C value. Simple dosing algorithms for a basal analog (Table 4)[23] and premixed insulin analog (Table 5)[43] have been developed.

Despite which algorithm is used, the dose is titrated based on results from self-monitoring of fasting plasma glucose until glycemic goals are met.[43,44] If treatment goals are not achieved within 1 week, an additional 1 to 3 units for every 50 mg/dL that pre-meal glucose exceeds the target level should be added. Doses should be reduced by a similar amount if glucose levels are too low or the patient experiences hypoglycemia.[43,44] Intensification of insulin therapy may not be appropriate for all patients. Those with a short life expectancy, comorbidities, advanced complications of diabetes, the very young, or those who are prone to severe hypoglycemia represent examples of patients in whom moderate rather than tight glycemic control may be appropriate.[11]

Insulin analogs are more expensive than human insulin preparations, presumably because they represent a technological improvement over older insulin formulations. Out-of-pocket costs vary from formulation-to-formulation, and even the cost of the same analog may vary by pharmacy, insurance plan, and reimbursement factor. The 2- to 3-fold higher cost of an insulin analog compared to a human insulin may represent a barrier for some patients. For others, the improved predictability, tolerability, and flexibility of analogs may make the added expense more acceptable. As such, better adherence should ensue, and fewer complications may translate to cost benefits and fewer out-of-pocket medical expenses over the long-term.[74]

To choose from among the various insulin analogs, physicians should begin by deciding which of the 3 approaches to therapy suits the particular patient best. For example, if a basal insulin is to be added to oral therapy, how does one choose between insulin glargine and insulin detemir? Both have similar pharmacokinetic and time-action profiles, provide similar reductions in A1C, and are associated with a lower risk of hypoglycemia than NPH insulin. In virtually all clinical trials in which insulin detemir has
been studied, it has been associated with less weight gain than NPH. This effect has not consistently been observed with insulin glargine, and for patients concerned with weight gain, insulin detemir may thus be preferred.

If a rapid-acting insulin analog is to be added to mealtimes, or used in basal-bolus therapy, all 3 available formulations (aspart, lispro, glulisine) appear to have similar characteristics. Similarly, for patients who prefer the simplicity and convenience of premixes, BIAsp 30, lispro 75/25 (or 50/50), individual patient preference, lifestyle, or the availability of the particular premix in a particular pen device might guide the choice.

Overcoming Practical Barriers to Insulin Therapy

There are a number of practical barriers that must be overcome to effectively initiate insulin therapy in patients with type 2 diabetes and improve poor adherence that may occur when patients are transitioned to this treatment. The negative impact of regimen complexity on adherence to therapy in patients transitioning from oral to insulin therapy can be overcome by using any of the relatively simple treatment strategies described previously. Fear of needles can be overcome by reassuring patients that needles used today are much finer and that they are laser sharpened and silicone coated for ease of entry into the skin. Furthermore, insulin pens can improve patient acceptance by enhancing dosing accuracy and permitting faster and easier dosing changes compared with a vial and syringe; insulin pens have also been reported to be more convenient and discreet. A recent study comparing an insulin pen with vial and syringe use indicated that pens are more accurate and acceptable to patients, and require less training assistance. Although few comparative studies of pens have been conducted, 1 recent study of the FlexPen (Novo Nordisk) and OptiClik (sanofi-aventis) pen devices suggested that FlexPen was easier to use, easier to learn how to use, preferred by more patients, and less prone to dosing errors. These data are preliminary, however, and should be considered as such.

Fear of complications can be managed by appropriate patient education that emphasizes the benefits and lack of long-term complications associated with this treatment. The risk for hypoglycemia with insulin therapy has been substantially reduced by the advent of newer insulin analogs, and the risk for serious hypoglycemic episodes may also be reduced by making sure that the approach to insulin therapy fits with the patient’s lifestyle (eg, exercise regimen, work schedule, and meal times), and by appropriate patient education.

Conclusions

Type 2 diabetes is a progressive disease. At the time of diagnosis, patients should be informed that insulin therapy is part of the natural course of diabetes, and not a last resort to be feared or avoided. Although initial treatment may begin with oral agents, the vast majority will transition to insulin therapy to achieve and maintain good glycemic control. Insulin therapy has become more flexible and convenient with insulin analogs (which more closely mimic physiologic insulin secretion than human insulins) and better insulin delivery systems. Addition of once- or twice-daily administration of long-acting insulin analogs to OADs effectively lowers A1C in patients with an elevated FPG, and with less risk for hypoglycemia compared with NPH. Mealtime administration of rapid-acting insulin analogs decreases postprandial glucose excursions and lowers A1C. Premixed insulin analogs provide an effective and convenient approach to controlling FPG and PPG and lowering A1C levels in patients with type 2 diabetes transitioning to insulin therapy. The reduction in regimen complexity achieved with premixed insulin analogs has the potential to overcome an important barrier to successful insulin therapy. Compared to conventional insulins, the insulin analogs also decrease the risk for hypoglycemia, which can prevent patients from adhering to insulin-based regimens. Selection of appropriate insulin analogs and convenient injection devices can facilitate the transition to insulin therapy. Patient education about insulin, its potential benefits, and how to manage symptoms of hypoglycemia are also important for decreasing patient anxiety and optimizing adherence. Ultimately, a physician’s choice of insulin therapy should be individualized according to the patient’s glycemic parameters, treatment preferences, and lifestyle.
Acknowledgments

The author thanks Novo Nordisk for funding that helped support the preparation of this manuscript and Bob Rhoads for writing and editorial assistance.

Footnotes

Readers are encouraged to respond to Paul Blumenthal, MD, Deputy Editor of MedGenMed, for the editor’s eyes only or for possible publication via email: pblumen@stanford.edu

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Figures and Tables
Figure 1

Percent of patients reaching A1C ≤ 6.5% and < 7.0% in the 1-2-3 Study.[44]
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* 1-2 hours post-meal  
** 2 hours post-meal  
*** as close to normal as possible without undue risk of hypoglycemia
## Table 2

Noninsulin Pharmacotherapies for Management of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Insulin Secretagogues</th>
<th>Insulin Sensitizers</th>
<th>Other Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Metformin</td>
<td>alpha-Glucosidase Inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td></td>
<td>Acarbose</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Rosiglitazone</td>
<td>Miglitol</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Pioglitazone</td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>GLP-1 Analogs</td>
<td>*</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>Exenatide</td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td></td>
<td>DPP-IV Inhibitors</td>
</tr>
<tr>
<td>Glinides</td>
<td>Sitagliptin</td>
<td></td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Amylin Analog</td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Pramlintide</td>
<td></td>
</tr>
</tbody>
</table>

Combination products are also available, most of which combine a secretagogue with a sensitizer; several other agents in this class are in clinical development.
### Table 3
Comparison of Insulin Preparations by Pharmacodynamics and Cost

<table>
<thead>
<tr>
<th>Insulin Preparation</th>
<th>PD Parameters</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset (h)</td>
<td>T&lt;sub&gt;peak activity&lt;/sub&gt; (h)</td>
</tr>
<tr>
<td><strong>Rapid-acting analogs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>0.17-0.33</td>
<td>1-3</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>0.25</td>
<td>0.5-1.5</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>0.25-0.5</td>
<td>0.5-2.5</td>
</tr>
<tr>
<td><strong>Short-acting human</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular human Insulin (RHI)</td>
<td>0.5-1</td>
<td>1-5</td>
</tr>
<tr>
<td><strong>Intermediate-acting human</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral protamine Hagedorn (NPH)</td>
<td>1-2</td>
<td>6-14</td>
</tr>
<tr>
<td><strong>Long-acting analogs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>0.8-2</td>
<td>6-8</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>1.1</td>
<td>2-20</td>
</tr>
<tr>
<td><strong>Premixes (human)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH/RHI 70/30 or 50/50</td>
<td>0.5</td>
<td>1.5-12</td>
</tr>
<tr>
<td><strong>Premixes (analogs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biphasic insulin aspart 70/30</td>
<td>0.17-0.33</td>
<td>1-4</td>
</tr>
<tr>
<td>Insulin lispro 75/25</td>
<td>0.25-0.5</td>
<td>≤ 2</td>
</tr>
<tr>
<td>Insulin lispro 50/50</td>
<td>0.25-0.5</td>
<td>0.5-1.5</td>
</tr>
<tr>
<td>Inhaled insulin</td>
<td>0.17-0.33</td>
<td>0.5-1.5</td>
</tr>
</tbody>
</table>

*Except for pen devices, does not include the cost of the needles and syringes, or, in the case of inhaled insulin, the inhaler, chamber, or release unit that must be replaced every 2 weeks; **unless otherwise noted; ***approximately equivalent to 990 units of RHI (ie, one 10-mL vial of 100 unit/mL); pharmacodynamic data from respective prescribing information. Cost data from Red Book 2006[83] and www.drugstore.com, accessed December 14, 2006. Prices are for comparison and could vary considerably, depending on source.
### Table 4

Starting and Titration Schedule for a Basal Insulin Analog

<table>
<thead>
<tr>
<th>Self-Monitored FPG (mg/dL)</th>
<th>Dosage Increase (units/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 180</td>
<td>8</td>
</tr>
<tr>
<td>≥ 140 to &lt; 180</td>
<td>6</td>
</tr>
<tr>
<td>≥ 120 to &lt; 140</td>
<td>4</td>
</tr>
<tr>
<td>&lt; 100 to &lt; 120</td>
<td>2</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose; *no increase if FPG is < 72 mg/dL in the preceding week; decrease dosage (2-4 units/day) if FPG is < 56 mg/dL or severe hypoglycemia (requiring assistance) occurred within the preceding week; copyright 2003 American Diabetes Association. From Diabetes Care 2003;26:3080-3086; reprinted with permission from The American Diabetes Association.
### Table 5

Starting and Titration Schedule for a Premixed Insulin Analog

<table>
<thead>
<tr>
<th>Blood Glucose Values</th>
<th>Starting Dose</th>
<th>Dose Titration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG &lt; 180 mg/dL</td>
<td>5 units before breakfast and supper</td>
<td></td>
</tr>
<tr>
<td>FPG ≥ 180 mg/dL</td>
<td>6 units before breakfast and supper</td>
<td></td>
</tr>
<tr>
<td>After Initial Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG &lt; 80 mg/dL</td>
<td>Reduce by 2 units</td>
<td></td>
</tr>
<tr>
<td>FPG 80-110 mg/dL</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>FPG 111-140 mg/dL</td>
<td>Increase by 2 units</td>
<td></td>
</tr>
<tr>
<td>FPG 141-180 mg/dL</td>
<td>Increase by 4 units</td>
<td></td>
</tr>
<tr>
<td>FPG &gt; 180 mg/dL</td>
<td>Increase by 6 units</td>
<td></td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose;

*increase in total daily dose should not exceed the greater of 10 units or 10% of the total daily dose; morning dose is based on pre-supper blood glucose reading; supper dose is based on pre-breakfast blood glucose reading; the dose titration is based on blood glucose values from the preceding 3 days; reprinted from Rolla AR, Rakel RE. Practical approaches to insulin therapy for type 2 diabetes mellitus with premixed insulin analogues. Clin Ther. 2005;27:1113-1125, with permission from Excerpta Medica, Inc.