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Integrating Advances in Insulin into Clinical Practice

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LEARNING OBJECTIVES

- Compare the clinical pharmacology of the basal and prandial analog and human insulins
- Describe the benefits and limitations of insulin in combination with incretin-based therapies
- Provide an overview of the clinical pharmacology of insulin degludec and pegylated lispro
- Describe strategies to improve communication, collaboration, and education of patients when initiating basal or prandial insulin

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Integrating Advances in Insulin into Clinical Practice

Introduction……S2

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The prevalence of diabetes mellitus continues to rise in the United States, increasing from an estimated 17.9 million people in 2003-2006 to 18.8 million in 2010.[1,2] Despite decreases in the prevalence of smoking, elevated cholesterol, and high blood pressure from 1988 to 2008, the number of people diagnosed with dysglycemia and obesity increased within the same timeframe.[3] Over the past 25 years, the percentages of men and women who achieved a glycated hemoglobin (HbA_{1c}) level <7.0% declined, decreasing to 38.4% and 57.1%, respectively, in 2007-2008. Also during the past 25 years, the percentages of men and women with impaired fasting glucose (IFG) or diabetes mellitus has risen, affecting 62% of men and 43% of women in 2007-2008. Some estimates predict that, by 2020, 77% of men and 53% of women could have IFG or diabetes mellitus.[3]

The rise in the prevalence of diabetes is modestly offset by small increases in the percentage of individuals diagnosed with diabetes who have attained acceptable glycemic control. Nonetheless, inadequate treatment of diabetes remains a major therapeutic challenge as 45% of those diagnosed with diabetes have not achieved an HbA_{1c} level <7.0%, the goal recommended for most people with diabetes mellitus by the American Diabetes Association (ADA).[4] Furthermore, during 2007-2010, 12.9% of US adults with a self-reported diagnosis of diabetes exhibited poor glycemic control, as evidenced by an HbA_{1c} level >9.0%. Other cardiovascular risk factors are poorly controlled in these patients as well. During 2003-2006, only 10.2% of people with type 2 diabetes simultaneously achieved their target HbA_{1c} level, low density lipoprotein-cholesterol level, and blood pressure goals.[5]

Despite the increased prevalence and inadequate treatment of diabetes, 1 in 6 people diagnosed with diabetes in the United States receives no medication.[2] In addition, despite being universally effective, only one-quarter of people with diabetes are treated with insulin.[2,6] The underutilization of insulin is also demonstrated by the fact that nearly half the patients treated with insulin, either alone or in combination with oral agents, have an HbA_{1c} level >9.0%.[7] Factors that contribute to the underutilization of insulin include concerns regarding hypoglycemia and weight gain, perceived treatment complexity, and feelings of failure.[8,9] The analog insulins are preferred over human insulins.[6,10] The time-action profiles of the rapid-acting insulin analogs are more predictable than regular human insulin.[10] Compared with neutral protamine Hagedorn insulin, the long-acting insulin analogs provide a fairly flat time-action profile over 24 hours, with better reproducibility and consistency between and within patients. These characteristics result in a reduction in the risk of hypoglycemia with the long-acting insulin analogs.[10] Yet many challenges to both health care providers (HCPs) and patients remain with regard to initiation of insulin treatment; these limit insulin's role in the management of patients with type 2 diabetes. Since most patients with diabetes are managed in the primary care setting, these are important issues for HCPs and their patients to address.[11]

The goal of this supplement is to provide insight into the continuing evolution of insulin and to provide solutions to the challenges faced in managing patients taking insulin in the primary care setting. Insulin formulations (excluding premixed formulations) currently available in the United States are shown in the **TABLE**.

TABLE Prandial and basal insulins currently available in the United States

Generic Name	Trade Name
Prandial Insulins	
Aspart	NovoLog
Glulisine	Apidra
Lispro	Humalog
Regular human	Humulin R, Novolin R
Basal Insulins	
Detemir	Levemir
Glargine	Lantus
Neutral protamine Hagedorn	Humulin N, Novolin N

In the first article, Dr Andrew Rhinehart describes the evolution of insulin since its discovery nearly a century ago and discusses characteristics of different insulin formulations. Next, Dr Allen King discusses various advances in insulin therapy, including the use of insulin in combination with other glucose-lowering agents, particularly incretin-based therapy. In addition, Dr King describes new insulin formulations, such as insulin degludec and pegylated insulin lispro. In the final article, Drs Michael Heile and Timothy Reid discuss several strategies designed to engage the patient in a collaborative relationship with the HCP, with the goal of helping patients improve self-management with their insulin treatment. A series of case studies is provided to illustrate key concepts and to simplify integration into clinical practice.

It is our hope that you find this supplement, "Integrating Advances in Insulin into Clinical Practice," helpful in providing care to your patients with diabetes.

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Overview of Current Insulin Formulations

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Defects in both insulin secretion and function play a fundamental role in the pathophysiologic mechanisms underlying both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). As the most physiologic treatment option available, insulin plays a central role in the management of patients with T1DM and a growing role in the management of patients with T2DM, as is reflected in current treatment guidelines.[1,2]

EVOLUTION OF INSULIN FORMULATIONS

Since its discovery almost a century ago, insulin formulations have undergone a tremendous evolution in their sources and purity, with each generation offering important improvements in clinical utility, safety, and tolerability. Moving from animal-sourced insulin formulations to human insulins to analog insulins, the time-action profile has progressively moved closer to that of endogenous insulin, with less inter- and intrapatient variability in response. In addition, safety and tolerability have improved, particularly concerning reductions in overall and nocturnal hypoglycemia. In addition, less weight gain is possible. As a consequence, the analog insulins, although noted to be more costly, are generally preferred over human insulins, according to the recommendations of the American Association of Clinical Endocrinologists and the American Diabetes Association/European Association for the Study of Diabetes.[1,2]

Because endogenous insulin is secreted at a relatively constant rate over the course of the day, supplemented by short bursts in response to food, 2 broad classes of insulin have been developed. Basal insulins, which provide a relatively slow and consistent rate of absorption and a long duration of action to mimic pancreatic basal insulin secretion, are used to control overall glycemia while primarily reducing fasting hyperglycemia. Prandial (or bolus) insulins have a rapid onset and short duration of action to coincide with carbohydrate absorption and are used primarily to reduce postprandial hyperglycemia. The basal insulins currently available are the long-acting analogs insulin detemir and insulin glargine, as well as the intermediate-acting human insulin, neutral protamine Hagedorn (NPH). The prandial insulins currently available are the rapid-acting analogs insulin aspart, insulin glulisine, and insulin lispro, as well as the short-acting regular human insulin.

Human versus analog insulins

The human and analog insulins have been studied in numerous clinical trials to compare their pharmacokinetics and pharmacodynamics as well as efficacy and safety. Some of these have involved the euglycemic clamp technique, which measures insulin absorption and insulin activity through simultaneous intravenous infusion of insulin and glucose to maintain a constant glucose level. Rather than directly measuring the biologic activity of insulin, the euglycemic clamp technique measures surrogate markers such as the maximum plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}).

Basal insulins

The preference for insulin detemir and insulin glargine over NPH insulin is based on pharmacokinetic and pharmacodynamic trials and clinical efficacy trials, as well

as the experience of experts.[1,2] The pharmacokinetics and pharmacodynamics of basal insulins have been assessed in several clinical trials involving patients with T1DM or T2DM. In patients with T1DM, the intrapatient variability in both the metabolic activity and duration of action were significantly less with insulin detemir and insulin glargine than with NPH insulin. Furthermore, NPH was associated with a more pronounced peak over 24 hours and a shorter duration of action (**FIGURE**).[3,4]

In patients with T2DM, metabolic activity was significantly greater for insulin glargine than insulin detemir or NPH insulin.[5] Endogenous glucose production decreased after administration of each of the 3 basal insulins, with no significant difference between either of the basal insulin analogs and NPH. For NPH insulin, this was followed by increased endogenous glucose production 10 to 11 hours later, leading to a significant rise in plasma glucose levels. A separate study showed comparable time-action profiles and duration of action for insulin detemir and insulin glargine.[6] Intrapatient variability in the dose-response was significantly lower with insulin detemir compared with insulin glargine, while there was no difference between subjects.

Although some variation exists among these and similar trials, the results suggest greater metabolic activity over a longer period of time with glargine and detemir than with NPH.[7,8] Therefore, once-daily dosing with insulin detemir or insulin glargine is more likely to provide glycemic control than once-daily NPH insulin. In addition, the lower intrapatient variability observed with the basal insulin analogs may serve to lower the risk of hypoglycemia compared with NPH insulin.

Efficacy and safety of basal insulins

Two recent reviews generally confirmed the results of pharmacokinetic and pharmacodynamic studies showing clinically important differences in efficacy and safety between NPH insulin and insulin glargine or insulin detemir.[9,10]

A pooled analysis of data from 5 randomized controlled trials with similar designs found that patients with T2DM aged ≥65 years treated with insulin glargine achieved greater reductions in glycated hemoglobin (HbA_{1c}) and fasting blood glucose than those receiving similar doses of NPH insulin.[9] For patients aged <65 years, there was no significant difference in reductions in HbA_{1c} or fasting blood glucose. There was no difference between treatments with respect to daytime symptomatic and daytime severe hypoglycemia. The incidence rates of nocturnal symptomatic hypoglycemia (20% vs 34%; $P = .008$) and nocturnal severe hypoglycemia (0.8% vs 2.2%; $P = .007$) were significantly lower in patients treated with insulin glargine than with NPH insulin, respectively. Patients aged <65 years treated with insulin glargine had lower incidence and event rates of nocturnal symptomatic hypoglycemia (20% vs 34%, $P = .005$; 1.27 vs 2.78 events/patient-year, $P = .03$) and severe hypoglycemia (0.7% vs 2.2%, $P = .01$; 0.02 vs 0.07 events/patient-year, $P = .007$) than those receiving NPH insulin, respectively.

For insulin detemir, a systematic review included 9 clinical trials in adults with T1DM and 5 clinical trials in adults with T2DM; all trials were 12 weeks or longer in duration. In patients with T1DM, insulin detemir and NPH insulin were found to provide similar HbA_{1c} reduction, while fasting plasma glucose (FPG) reduction was greater with insulin detemir.[10] Significantly lower variability in FPG was observed with insulin detemir than with NPH insulin. The frequency of overall hypoglycemia was found to be similar or lower with insulin detemir, while nocturnal hypoglycemia was significantly less common with insulin detemir than with NPH insulin. In each trial, NPH insulin was associated with weight gain, while insulin detemir was associated with either modest weight gain, weight loss, or no change in the same clinical trials.

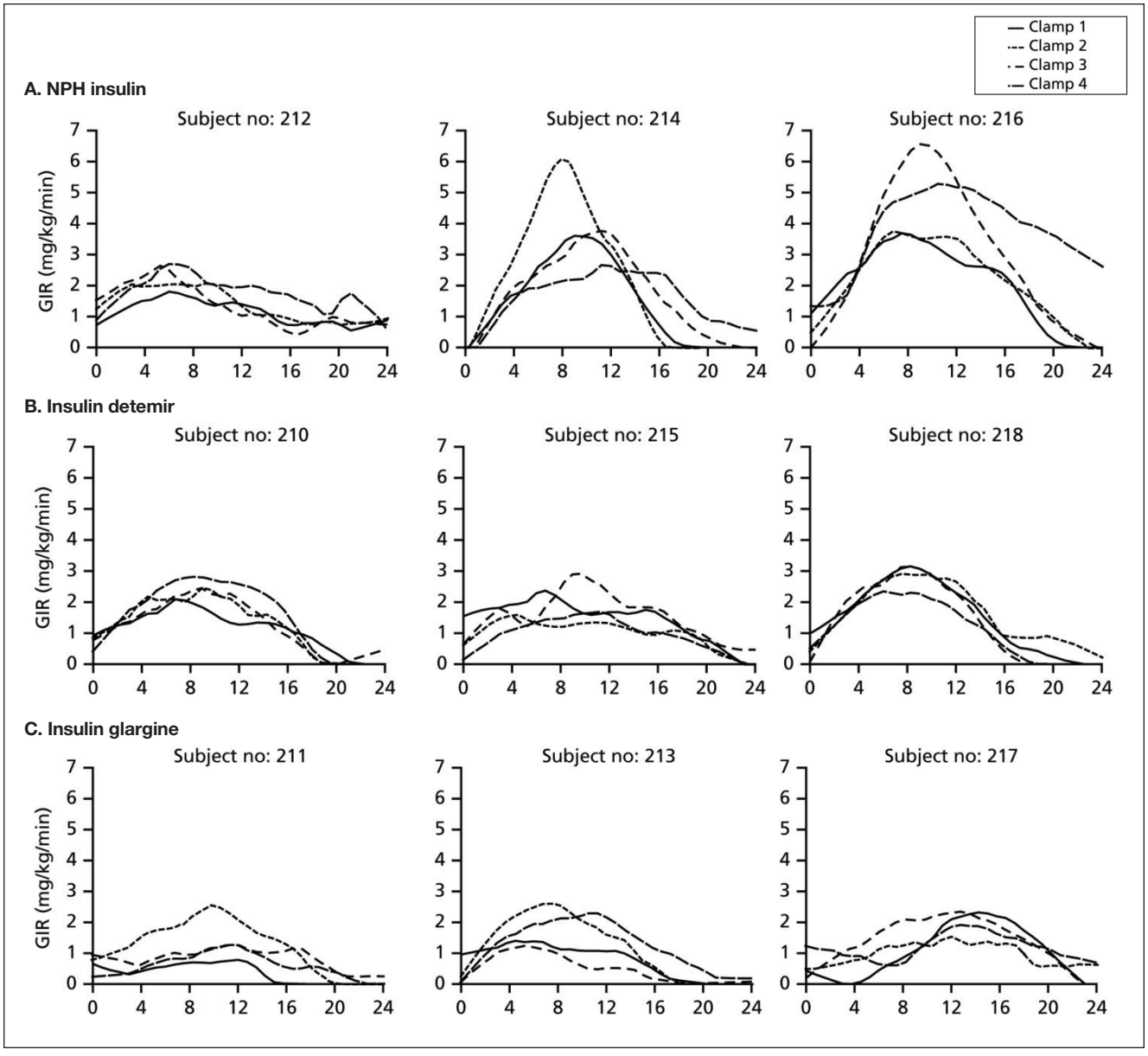
In patients with T2DM, HbA_{1c} reduction and FPG reduction were found to be similar with insulin detemir and NPH insulin.[10] Variability in blood glucose control with insulin detemir was lower in 3 of the studies and similar to NPH insulin in the other 2. Overall and nocturnal hypoglycemia were found to be significantly less frequent with insulin detemir than with NPH insulin in 4 of the 5 studies.

Rapid-acting insulin analogs (aspart, glulisine, and lispro) have a significantly more rapid onset, shorter duration of action, and less pharmacodynamic variability than regular human insulin.

Prandial insulins

Pharmacokinetic and pharmacodynamic investigations more than a decade ago indicated that the rapid-acting insulin analogs (aspart, glulisine, and lispro) have a significantly more rapid onset, shorter duration of action, and less pharmacodynamic variability than regular human insulin (RHI).[11-13] Similar results are generally observed in randomized, double-blind clinical trials. With respect to the rapid-acting insulin analogs, the more rapid onset of action compared with RHI results in significantly lower postprandial glucose excursions.[14-21]

FIGURE **Representative glucose infusion rates over time (time-action profiles) of patients administered (A) NPH insulin, (B) insulin detemir, or (C) insulin glargine[3]**



GIR, glucose infusion rate; NPH, neutral protamine Hagedorn.

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Postprandial hyperglycemia is an important treatment target, not only because it contributes more than fasting hyperglycemia to glycemic control at HbA_{1c} levels <8%, but also because higher postprandial hyperglycemia has been more closely associated as a risk factor for cardiovascular morbidity and mortality than FPG.[22,23] The shorter duration of action and lower intrapatient variability observed with the rapid-acting insulin analogs compared with RHI contribute to a generally lower incidence of hypoglycemia, including nocturnal hypoglycemia.[14-21,24] A Cochrane review found a higher median incidence of severe hypoglycemia with RHI compared with prandial insulin analogs in patients with T1DM (46.1 vs 21.8 episodes/100 patient-years) or T2DM (1.4 vs 0.3 episodes/100 patient-years), respectively.[25] Gen-

erally similar glycemic results have been observed when patients received all-analog basal-bolus therapy compared with all-human insulin or analog-human basal-bolus therapy.[26-28]

Comparisons of rapid-acting analogs and human insulin as biphasic or premixed formulations also show improved postprandial glycemic control and reduced nocturnal hypoglycemia with biphasic analog insulin compared with biphasic human insulin.[29-34] A meta-analysis of 9 randomized trials found no significant difference between biphasic analog insulin and biphasic human insulin in HbA_{1c} reduction, while postprandial glucose levels after breakfast, lunch, and dinner were significantly lower with biphasic analog insulin (end of treatment difference [ETD], –6 mg/dL; $P < .01$).[35] In contrast, reductions in FPG were significantly greater with biphasic human insulin (ETD, –11 mg/dL; $P < .01$). The meta-analysis also showed that, while rates of overall hypoglycemia were similar between treatments, the rate of nocturnal hypoglycemia was 50% lower with biphasic analog insulin ($P < .01$), while the rate of daytime hypoglycemia was 24% lower with biphasic human insulin ($P < .01$). The rate of major hypoglycemia was 55% lower with biphasic analog insulin ($P < .05$).

> The insulin analogs have enabled more patients with T1DM or T2DM to more safely achieve glycemic targets and are generally recommended over human insulins.

COMPARISON AND LIMITATIONS OF CURRENT INSULIN ANALOGS

While there have been progressive improvements with insulin formulations through the decades, insulin analogs are not without limitations. With regard to the basal insulin analogs, a recent Cochrane review found no clinically important differences between insulin detemir and insulin glargine regarding glycemic control or overall, nocturnal, and severe hypoglycemia; insulin detemir was, however, associated with less weight gain.[36] Most patients achieve HbA_{1c} ≤7.0% with basal insulin analog therapy, although administration of insulin detemir more frequently and at a higher dose may sometimes be required to achieve the same glycemic control as insulin glargine, especially in patients with T1DM.[36] This may result from the lower metabolic potency with insulin detemir compared with insulin glargine.[37]

Hypoglycemia, including nocturnal hypoglycemia, occurs at a similar rate with insulin detemir and insulin glargine and is generally mild or moderate in nature.[36,38-42] The rates of overall hypoglycemia range from 5.8 to 19.3 episodes/patient-year for insulin detemir and 6.2 to 17.9 episodes/patient-year for insulin glargine, while the respective rates for nocturnal hypoglycemia are 1.3 to 4.2 episodes/patient-year and 1.3 to 3.4 episodes/patient-year.[38,39] Weight gain is common, although there is less weight change associated with insulin detemir than with insulin glargine (–0.49 kg to 2.8 kg vs 1.0 kg to 3.8 kg, respectively).[38-42] While some intrapatient variability exists with regard to glucose-lowering effect, it is generally lower with insulin detemir than with insulin glargine.[37]

Regarding the prandial insulin analogs, no clinically important differences were noted among insulin aspart, insulin glulisine, and insulin lispro in a Cochrane review.[25] This is consistent with a recent study involving 14 healthy volunteers who underwent an 8-hour euglycemic clamp study following administration of 0.15 units/kg.[43] Total exposure was comparable among the 3 prandial insulin analogs. The mean onset of action was 47 minutes for glulisine, 51 minutes for lispro, and 58 minutes for aspart, while the respective mean t_{max} values were 80, 68, and 86 minutes. The mean durations of action were 189, 194, and 194 minutes for glulisine, lispro, and aspart, respectively. The incidence of hypoglycemia was similarly low among the 3 prandial insulin analogs.

CONCLUSION

The basal and prandial insulin analogs represent improvements over earlier insulins, particularly with respect to reduced hypoglycemia, weight gain, and a time-action profile that more closely parallels endogenous insulin. Consequently, the insulin analogs have enabled more patients with T1DM or T2DM to more safely achieve glycemic targets and are generally recommended over human insulins. However, concerns regarding treatment complexity and logistical constraints, as well as weight gain and symptomatic hypoglycemia, remain. ●

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Advances in Insulin Formulations

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DISCLOSURES
Dr King has disclosed that he is on the advisory boards for Novo Nordisk, Inc., and sanofi-aventis U.S. LLC.

The central role of insulin in the management of patients with type 1 diabetes mellitus (T1DM) remains, nearly a century after its first use in humans. In patients with type 2 diabetes mellitus (T2DM), the role of insulin has evolved as other therapies have been introduced, with insulin now used across the spectrum of the disease.[1,2] This article discusses the use of insulin in patients with T1DM or T2DM, including combined use with other agents in T2DM, with an emphasis on incretin-based therapies. In addition, new insulin products and concentrations are discussed along with their varied routes of administration.

INSULIN IN COMBINATION WITH INCRETIN-BASED THERAPIES

The progressive nature of T2DM requires ongoing intensification of therapy, such that most patients will eventually require insulin therapy, often in conjunction with other glucose-lowering agents.[1] While the use of insulin in combination with most glucose-lowering agents is well established, clinical experience with the combination of insulin and incretin-based therapies is increasing.

Incretin-based therapies

The glucose-dependent actions and low incidence of hypoglycemia with the glucagon-like peptide-1 receptor (GLP-1R) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors make incretin-based therapies attractive options for combination treatment with insulin. The weight loss effects of the GLP-1R agonists and weight neutral effects of the DPP-4 inhibitors are of added benefit. The GLP-1R agonists exenatide for twice daily administration (BID) and liraglutide for once daily administration, as well as the 4 DPP-4 inhibitors currently available (alogliptin, linagliptin, saxagliptin, sitagliptin), are approved for use with basal insulin in patients with T2DM (but not T1DM). Exenatide for once-weekly administration (QW) is not approved for use with insulin.

The combined use of incretin-based therapies and insulin is supported by several randomized clinical trials, most involving a GLP-1R agonist (**TABLE 1**).[3-7] These trials show that the addition of a GLP-1R agonist or DPP-4 inhibitor to insulin treatment resulted in significantly greater reductions in glycated hemoglobin (HbA_{1c}) levels compared with placebo; thus significantly more patients treated with an incretin in combination with insulin achieved HbA_{1c} <7.0%. The reduction in HbA_{1c} with exenatide was due to a significantly greater reduction in the postprandial glucose (PPG) level rather than the fasting plasma glucose (FPG) level.[3,4] Significant reductions in both the FPG and PPG levels associated with sitagliptin contributed to the significantly greater reduction in HbA_{1c} compared with placebo.[6] Major hypoglycemia (blood glucose <50 mg/dL requiring assistance) occurred in ≤1% of patients, suggesting that the glucose-dependent effects of incretin-based agents may blunt this adverse event sometimes observed with basal insulin.[1]

A subanalysis of the 30-week study by Buse et al[4] examined the effects of baseline characteristics on glycemic and weight responses when adding exenatide to insulin glargine; patients could also have been receiving metformin ± pioglitazone.[8] Compared with the addition of placebo, patients treated with the addition of exenatide to insulin glargine had greater HbA_{1c} reductions regardless of baseline HbA_{1c} levels

TABLE 1 **Major outcomes from clinical trials utilizing a combination of insulin and incretin-based therapy[3-7]**

Treatment	Design	Pre-study therapy	Change from baseline						Hypoglycemia		% of patients achieving HbA_{1c} <7.0%
			HbA_{1c} (%)	FPG (mg/dL)	PPG (mg/dL)			Body weight (kg)			
Metformin + insulin glargine to achieve FPG <100 mg/dL in combination with[3]:	SC, R, OL; 4 wks; N = 48	Basal insulin or metformin ± SU							Major[d]:	Minor (PYE)[e]:	
Exenatide 5 mcg BID x 2 wks, then 10 mcg BID x 2 wks or			–1.80	–12	606[b]			–0.9	0%	10.1	80.0%
Sitagliptin 100 mg orally QAM or			–1.49	–12	612[b]			0.1	0%	3.3	87.5%
Placebo			–1.23[a]	–5	728[b,c]			0.4[a]	0%	1.6	62.5%
Insulin glargine to achieve FPG <100 mg/dL ± metformin ± pioglitazone in combination with[4]:	MC, R; 30 wks; N = 259	Insulin glargine ± metformin ± pioglitazone			Morning:	Midday:	Evening:		Major[g]:	Minor[h]:	
Exenatide 5 mcg BID x 4 wks, then 10 mcg BID or			–1.74	–29	–36	–9	–29	–1.78	0%	25%	60%
Placebo			–1.04[f]	–27	–4[f]	–4	2[f]	0.96[f]	1%	29%	35%[f]
Metformin in combination with[5]:	MC, OL; 12-wk run-in followed by 26-wk OL,R for those not achieving HbA_{1c} <7.0% during run-in; N = 323 for 26 wk phase	Metformin + liraglutide 0.6 mg QD x 1 wk, then 1.2 mg QD x 1 wk, then 1.8 mg QD x 10 wks (run-in period)							Major[j]:	Minor (PYE)[k]:	
Liraglutide 1.8 mg QD or			0.02	–7	NR			–0.95	0%	0.029	17%
Liraglutide 1.8 mg QD + insulin detemir QHS to achieve FPG 72-108 mg/dL			–0.51[i]	–38[i]	NR			–0.16[a]	0%	0.286[i]	43%[i]

(P < .001). In addition, greater HbA_{1c} reductions were observed in exenatide-treated patients who had longer duration of diabetes and lower body mass index (BMI) (P < .01). Exenatide-treated patients lost more weight than placebo-treated patients irrespective of baseline HbA_{1c} or BMI (P < .05); those treated with exenatide with a longer duration of diabetes lost the most weight (P < .001).

Additional trials have investigated other endpoints using the combination of insulin and incretin-based therapy. One retrospective review of a national US insurance claims data-

TABLE 1 CONTINUED

Major outcomes from clinical trials utilizing a combination of insulin and incretin-based therapy[3-7]

Treatment	Design	Pre-study therapy	Change from baseline						Hypoglycemia		% of patients achieving HbA_{1c} <7.0%
			HbA1c (%)	FPG (mg/dL)	PPG (mg/dL)			Body weight (kg)			
Insulin[m] ± metformin in combination with[6]:	MC, R, DB; 24 wks; N = 641	Insulin[m] ± metformin							Major[n]:	Minor[o]:	
Sitagliptin 100 mg QD or			–0.6	–18.5	–30.9			0.1	0.6%	16%	13%
Placebo			0.0[f]	–3.5[f]	5.2[f]			0.1	0.3%	8%	5%[f]
Metformin in combination with[7]:	SC, R, OL; 26 wks	Metformin ± second oral agent			Break-fast:	Lunch:	Dinner:		Major[p]:	Minor (PYE)[q]:	
Insulin detemir QHS to achieve prebreakfast FPG 72-108 mg/dL + sitagliptin 100 mg QD or			–1.44	–66	159	157	168	–1.7	0%	0.52	45%
Sitagliptin 100 mg QD ± SU			–0.89[f]	–22[f]	189[a]	180[a]	184[a]	–0.8	0%	0.91	24%[f]

Abbreviations: BID, twice daily; DB, double-blind; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; MC, multicenter; NR, not reported; OL, open-label; PPG, postprandial glucose; PYE, events/patient-year; QAM, once daily in the morning; QD, once daily; QHS, once daily in the evening/bedtime; R, randomized; SC, single center; SU, sulfonylurea.

[a]*P* values versus incretin: $P < .05$.

[b]6-hour postprandial blood glucose excursion (mg/dL-h).

[c]$P = .0036$ vs exenatide and $P = .0008$ vs sitagliptin.

[d]Major: patient unable to self-treat episode.

[e]Minor: patient able to self-treat and blood glucose <50 mg/dL or if no blood glucose level available or if blood glucose ≥50 mg/dL with symptoms only.

[f]*P* values versus incretin: $P < .001$.

[g]Major: blood glucose <53 mg/dL resulting in loss of consciousness or seizure with prompt recovery in response to glucagon or glucose, or presumed hypoglycemia requiring third party assistance due to severe impairment of consciousness or behavior.

[h]Minor: signs or symptoms associated with hypoglycemia and blood glucose <54 mg/dL that was self-treated or resolved spontaneously.

[i]*P* values versus incretin: $P < .0001$.

[j]Major: required third party assistance irrespective of blood glucose level.

[k]Minor: blood glucose <56 mg/dL that was self-treated.

[l]*P* values versus incretin: $P < .005$.

[m]Long-acting, intermediate-acting, or premixed insulin.

[n]Major: requiring medical intervention or exhibiting markedly depressed level of consciousness, including loss of consciousness or seizure.

[o]Minor: those not requiring assistance or requiring nonmedical assistance of others.

[p]Major: patient unable to self-treat.

[q]Minor: patient able to self-treat and blood glucose <56 mg/dL with or without symptoms.

base examined the treatment persistence and glycemic control of the combination of insulin glargine and exenatide BID prescribed in either order or simultaneously.[9] Four hundred fifty-three patients with T2DM were followed for 1 year. The HbA_{1c} reduction was significantly less in the insulin glargine followed by exenatide (G-E) group (–0.4%) compared with the exenatide followed by insulin glargine (E-G) (–0.9%) and insulin glargine and exenatide simultaneously (G+E) (–1.2%)

groups. At the 1-year follow-up, treatment persistence of insulin glargine and exenatide was 68% vs 38.5% in the E-G group ($P < .0001$), 65% vs 45.1% in the G-E group ($P < .0001$), and 58% vs 45.1% in the G+E group ($P = .3094$), respectively. A pooled analysis of G-E and E-G patients over 24 months of follow-up showed that the HbA_{1c} decreased –0.7% and 33.0% of patients achieved HbA_{1c} ≤7.0%.[10] Body weight remained unchanged in the E-G group at 24 months compared with baseline suggesting that these patients may achieve HbA_{1c} goals without incurring additional significant weight gain with the addition of insulin glargine. Patients in the G-E group lost a mean of 2.5 kg, suggesting that the addition of exenatide may be useful for patients with suboptimal glycemic control on an established insulin glargine regimen. At month 24, the daily insulin glargine doses were 0.40 units for the E-G group and 0.47 units for the G-E group. The frequency of any type of hypoglycemia was similar in both groups.

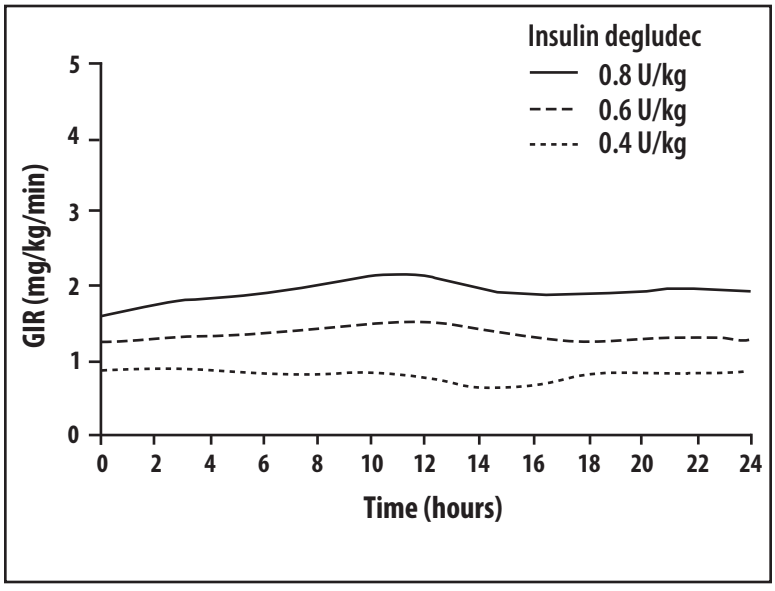
The addition of a GLP-1R agonist (either exenatide BID or liraglutide) (N = 61) to existing insulin therapy has been shown to result in significantly greater patient satisfaction over a mean of 7 months of treatment ($P < .001$).[11] At baseline, 52.5% had an insulin regimen consisting of multiple daily injections and 74% were receiving metformin. The addition of the GLP-1R agonist resulted in a reduction of HbA_{1c} levels (from 8.9% to 7.9%), body weight (111.1 kg to 104.0 kg), and total daily insulin dose (91 units to 52.2 units); all $P < .001$. Severe hypoglycemia, defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, occurred in only 1 patient.

In summary, the combined use of insulin and incretin-based therapy provides additional glycemic benefit beyond either agent alone with modest weight gain or loss. The addition of a GLP-1R agonist did not increase the rates of either severe or nonsevere hypoglycemia observed with basal insulin alone. These factors likely contributed to a high level of patient satisfaction compared with basal insulin alone. However, the need for additional daily injections with GLP-1R agonist therapy may have contributed to a low rate of persistence over 1 year when combined with insulin.

NEW BASAL INSULINS AND FORMULATIONS

Many advances have been made regarding the pharmacologic options for treating diabetes mellitus. However, since no currently available insulin therapy is without limitations, the development of additional basal insulin formulations continues.

FIGURE Glucose infusion rate mean profiles for insulin degludec at doses of 0.4, 0.6, or 0.8 U/kg at steady state[15]



GIR, glucose infusion rate.

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Insulin degludec

Clinical pharmacology

Insulin degludec is a novel basal insulin designed by modifying human insulin to prolong the time over which the insulin is released and reduce variability in the duration of action. Following subcutaneous injection, insulin degludec dihexamers reorganize into long chains of multihexamers that remain in solution at physiologic pH. These multihexamer chains slowly disassemble and release active insulin monomers that are continuously absorbed into the systemic circulation.[12,13]

Pharmacodynamics and pharmacokinetics

Clinical investigation of insulin degludec in euglycemic clamp studies has confirmed a duration of action >24 hours with a smooth and stable pharmacokinetic profile at steady state with low day-to-day intrapatient variability following subcutaneous administration. Once-daily dosing of insulin degludec does not lead to harmful accumulation (also called "stacking"), which is most often observed with prandial insulin and is associated with an increased risk of hypoglycemia.[14]

The pharmacodynamic activity of insulin degludec has been investigated in patients with T2DM or T1DM. Patients with T2DM (N = 49) were treated with insulin degludec 0.4, 0.6, or 0.8 units/kg once daily for two 6-day periods with a washout period between.[15] The mean glucose infusion rate profiles were flat and stable for all 3 dose levels (**FIGURE**). The glucose-lowering effect was evenly distributed over

the 24-hour dosing interval such that each 6-hour interval accounted for approximately 25% of the total 24-hour effect. In patients with T1DM (N = 54), pharmacodynamic variability of the total metabolic effect has been assessed.[16] Over 24 hours, the coefficient of variation was 20% for insulin degludec and 82% for insulin glargine ($P < .0001$). The intrapatient variability was consistently lower with insulin degludec compared with insulin glargine over 2-hour intervals through 24 hours: 0 to 24 hours (23% vs 72%, respectively; $P < .0001$), 0 to 2 hours (33% vs 60%, respectively), 10 to 12 hours (32% vs 135%, respectively), and 22 to 24 hours (33% vs 115%, respectively).

Pharmacokinetic investigations have shown insulin degludec to have a terminal elimination half-life of approximately 25 hours at steady state.[15,17] Furthermore, at steady state, the total exposure to insulin degludec was unchanged from day to day over a period of 10 days.[14]

Clinical trial experience

Several phase 3 noninferiority clinical trials have been conducted comparing insulin degludec with insulin glargine. Because of the differences in devices used to administer insulin degludec and other insulins, the clinical trials were open-label.[18-20]

Efficacy

In one study, adults with T1DM who had not achieved adequate glycemic control with basal-bolus insulin therapy for at least 1 year were randomized to insulin degludec or insulin glargine once daily in combination with insulin aspart at mealtime.[18] Insulin degludec was administered with the evening meal and insulin glargine was administered anytime during the day but at the same time every day. Using a treat-to-target approach, the basal insulin dose was titrated to achieve a prebreakfast blood glucose of 70 to 90 mg/dL, while the insulin aspart dose was titrated to achieve a preprandial and bedtime blood glucose of 70 to 90 mg/dL. After 52 weeks, the HbA_{1c} decreased 0.40% for insulin degludec and 0.39% for insulin glargine, demonstrating noninferiority of insulin degludec to insulin glargine in terms of glycemic control. In addition, the FPG decreased 23 mg/dL in the insulin degludec group and 25 mg/dL in the insulin glargine group ($P = .35$). HbA_{1c} <7.0% at the end of 52 weeks of treatment was achieved by 40% of patients treated with insulin degludec and 43% of patients treated with insulin glargine.

Two phase 3 clinical trials enrolled adults with T2DM with a baseline HbA_{1c} of 7% to 11% and a BMI ≤42 kg/m^2.[19,20] Patients were treated for 52 weeks. In 1 trial, insulin-naive patients with T2DM were randomized to insulin degludec or insulin glargine.[19] Most patients continued metformin and 2% continued a DPP-4 inhibitor. Basal insulin was titrated to achieve prebreakfast blood glucose of 70 to 90 mg/dL. After 52 weeks, the reduction in the HbA_{1c} was 1.06% with insulin degludec and 1.19% with insulin glargine, demonstrating noninferiority of insulin degludec to insulin glargine. Mean FPG levels decreased 68 mg/dL with insulin degludec and 59 mg/dL with insulin glargine ($P = .005$). Similar proportions of patients achieved HbA_{1c} levels <7.0% with insulin degludec (52%) and insulin glargine (54%). Mean insulin doses were similar in the 2 groups at week 1 and at the end of treatment.

In a basal-bolus trial, patients with T2DM who had been treated with insulin for at least 3 months, with or without oral glucose-lowering agents, were randomized to once daily administration of insulin degludec at the evening meal or insulin glargine anytime during the day but at the same time every day.[20] Basal insulin doses were titrated to achieve prebreakfast blood glucose of 70 to 90 mg/dL. Patients also received mealtime insulin aspart and continued metformin, pioglitazone, or both. After 52 weeks, the reduction in the HbA_{1c} was 1.10% with insulin degludec and 1.18% with insulin glargine, demonstrating noninferiority of insulin degludec to insulin glargine. Mean FPG levels decreased by 41 mg/dL with insulin degludec and 36 mg/dL with insulin glargine ($P = .1075$). Similar proportions of patients achieved HbA_{1c} levels <7.0% with insulin degludec (49%) and insulin glargine (50%).

Safety and tolerability

Hypoglycemia

In the 3 phase 3 clinical trials of patients with T1DM or T2DM and involving insulin degludec, overall confirmed hypoglycemia was defined as a blood glucose <56 mg/dL with or without symptoms, or severe episodes requiring assistance. Nocturnal confirmed hypoglycemia was defined as hypoglycemia that occurred from midnight to 6 AM.[18-20]

In patients with T2DM, overall confirmed hypoglycemia occurred at differing rates in patients treated with insulin degludec compared with insulin glargine (**TABLE 2**).[19,20] The wide range of hypoglycemia reported reflects differences in progression of disease, background oral agents used, and addition of bolus insulin to some regimens. Rates of nocturnal confirmed hypoglycemia and severe hypoglycemia differed between insulin degludec and insulin glargine as well. In previously insulin-naive patients with T2DM, 42% of insulin degludec patients and 46% of insulin glargine patients achieved HbA_{1c} <7.0% without overall confirmed hypoglycemia.[19] The percentage of patients who achieved HbA_{1c} <7.0% without nocturnal confirmed hypoglycemia was also similar.[19] The results of this trial suggest similar rates of overall confirmed hypoglycemia, but with a significantly lower rate of nocturnal confirmed hypoglycemia for insulin degludec vs insulin glargine. A preplanned, prospective meta-analysis

TABLE 2 **Rates of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin degludec or insulin glargine (events/patient-year)[19,20]**

	Insulin-naive			Previous insulin		
Hypoglycemia	**Insulin degludec**	**Insulin glargine**	***P* value**	**Insulin degludec**	**Insulin glargine**	***P* value**
Overall confirmed	1.52	1.85	.106	11.09	13.63	.0359
Nocturnal confirmed	0.25	0.39	.038	1.39	1.84	.0399
Severe	0.003	0.023	.017	.06	.05	–[a]

[a]Insufficient episodes for statistical comparison.

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of the phase 3 trials showed a 17% lower rate of overall confirmed hypoglycemia and a 32% lower rate of nocturnal confirmed hypoglycemia in the overall T2DM population treated with insulin degludec compared with insulin glargine. An 86% lower rate of severe confirmed hypoglycemia occurred in insulin-naive patients treated with insulin degludec compared with insulin glargine.[21]

In patients with T1DM, overall confirmed hypoglycemia occurred at a rate of 42.54 events/patient-year in patients treated with insulin degludec and 40.18 events/patient-year in patients treated with insulin glargine.[18] Rates of nocturnal confirmed hypoglycemia were 4.41 events/patient-year with insulin degludec and 5.86 events/patient-year with insulin glargine. In the same preplanned, prospective meta-analysis of the phase 3 trials, the rate of nocturnal confirmed hypoglycemia was 25% lower with insulin degludec compared with insulin glargine during maintenance treatment (weeks 16-52).[21]

Another meta-analysis was conducted involving patients with T1DM or T2DM who achieved HbA_{1c} <7.0%. Across 7 phase 3 clinical trials (N = 4330), data from the maintenance period showed a 21% lower rate of overall confirmed hypoglycemia and a 43% lower rate of nocturnal confirmed hypoglycemia with insulin degludec vs insulin glargine.[22]

The lower rates of hypoglycemia observed in clinical trials with insulin degludec compared with insulin glargine are consistent with the pharmacodynamic and pharmacokinetic profiles of each agent. As discussed previously, insulin degludec has a stable, peakless glucose-lowering effect that extends beyond 24 hours, but does not lead to accumulation following attainment of steady state concentration within 2 to 3 days. Furthermore, intrapatient variability is lower for insulin degludec than for insulin glargine.

Body weight

A small increase in total body weight is observed in patients with T1DM treated with insulin degludec averaging 1.8 kg over 52 weeks compared with 1.6 kg with insulin glargine ($P = .62$).[18] In patients with T2DM, the change in body weight ranged from 2.4 to 3.6 kg with insulin degludec over 52 weeks compared with 2.1 to 4.0 kg with insulin glargine (P = NS).[19,20]

Cardiovascular safety

While not designed to monitor cardiovascular outcomes, analysis of data from 16 phase 3 clinical trials showed a similar incidence rate for major adverse cardiovascular events (MACE), a composite of cardiovascular death, stroke, and acute coronary syndrome (myocardial infarction and unstable angina pectoris), for patients treated with insulin degludec or insulin degludec/insulin aspart and those treated with comparators (1.48 vs 1.44 events/100 patient-years, respectively; hazard ratio, 1.097).[23] In both treatment groups, patients with preexisting cardiovascular disease had a higher risk of experiencing a MACE than patients without preexisting cardiovascular disease. No clinically relevant differences in vital signs, electrocardiogram, corrected QT interval, and lipids were observed between the insulin degludec and insulin degludec/insulin aspart and comparator groups.

Further post-hoc analysis that included additional trials (including extension trials), but excluded unstable angina pectoris from the MACE composite endpoint, yielded incidence rates of 1.41 MACE events/100 patient-years for patients treated with insulin degludec or insulin degludec/insulin aspart and 0.90 MACE events/100 patient-years for those treated with comparators, yielding a hazard ratio of 1.614. However, data from the extension trials represented only 35% of the original randomized population and provided 2-year cardiovascular outcome data on approximately 12% of the insulin degludec population. Because these data were considered less robust than data from the original trials, a subsequent post-hoc analysis excluded the data from the extension trials. This analysis resulted in MACE rates of 1.51 events/100 patient-years with insulin degludec or insulin degludec/insulin aspart compared with 1.49 events/100 patient-years for comparators (hazard ratio 1.125). Since

these analyses neither confirm nor exclude increased cardiovascular risk with insulin degludec or insulin degludec/insulin aspart, further investigation is ongoing. Additional cardiovascular data from a dedicated cardiovascular outcomes trial has been requested by the US Food and Drug Administration before review of the new drug application for insulin degludec or insulin degludec/insulin aspart can be completed.[24] Insulin degludec has been approved in several countries in the European Union and Japan without a requirement of additional cardiovascular data.

Dosing flexibility

As noted earlier, the pharmacodynamic and pharmacokinetic profiles of insulin degludec were hypothesized to allow for more flexible once-daily dosing times. One trial involving 687 patients with T2DM randomly assigned patients to insulin degludec once daily with the evening meal (IDeg QD), or insulin degludec once daily with the administration time alternating between morning and evening to create intervals of 8 to 40 hours between insulin doses (IDeg QD Flex), or insulin glargine once daily at the same time each day.[25] Mean final insulin doses were 0.6 units/kg in all 3 groups. At 26 weeks, HbA_{1c} was reduced by 1.07% in the IDeg QD group, 1.28% in the IDeg QD Flex group, and 1.26% for the insulin glargine group. These results demonstrate noninferiority of IDeg QD Flex with insulin glargine in lowering HbA_{1c}. Fasting plasma glucose reductions were significantly greater with IDeg QD Flex compared with insulin glargine (end of treatment difference 8 mg/dL; $P = .04$); there was no difference in FPG reductions between the IDeg QD Flex and IDeg QD groups. The overall confirmed hypoglycemia rates were similar in the 3 groups (3.6 vs 3.6 vs 3.5 events/patient-year in the IDeg QD, IDeg QD Flex, and insulin glargine groups, respectively). Rates of nocturnal confirmed hypoglycemia were similar in all 3 groups. Two episodes of severe hypoglycemia occurred in each group. Adverse event rates were similar in all 3 groups.

These results suggest flexibility in the daily dosing time of insulin degludec is possible, for example, allowing a dose missed in the morning to be given at night. This is an advantage compared with other basal insulins that are recommended to be given the same time each day. If confirmed, this flexibility would enable patients to more easily incorporate insulin therapy with insulin degludec into their schedules, which should improve long-term treatment adherence.

Quality of life

Several published trials have assessed the impact of insulin degludec on quality of life using the Health-Related Quality of Life (Short-Form 36) questionnaire. A meta-analysis was conducted using patient-level data from 3 open-label, randomized, treat-to-target trials.[26] Insulin-naive patients with T2DM received insulin degludec or insulin glargine once daily for 26 or 52 weeks in combination with oral glucose-lowering drugs. At study end, patients treated with insulin degludec showed significant improvement in several physical health and mental health domains compared with insulin glargine, specifically significantly less bodily pain, better vitality, and overall physical health. The improvements in these domains contributed to an overall improvement in quality of life for patients taking insulin degludec compared with insulin glargine, particularly with long-term treatment. However, the open-label design of these studies and the fact that issues beyond glucose control and hypoglycemic events impact quality of life, warrant further investigation to fully assess the impact of insulin degludec on patients' quality of life.

In summary, insulin degludec is a new basal insulin with ultra-long duration of action with a unique formulation that provides flat and stable glucose-lowering activity longer than 24 hours, thereby providing flexibility in regard to dosing time. Reductions in HbA_{1c} and FPG with insulin degludec are similar to other basal insulin analogs, while the rates of overall and nocturnal confirmed hypoglycemia are significantly lower with insulin degludec. Some clinically important improvements in patient quality of life are observed for patients taking insulin degludec. Overall, insulin degludec offers several improvements compared with current basal insulin analogs that may lessen challenges associated with insulin therapy and improve adherence, while providing comparable glycemic control and improved safety.

Pegylated lispro

Clinical pharmacology

Insulin lispro is a rapid-acting insulin analog used for the control of postprandial hyperglycemia. A drawback of exogenously administered insulin is that it is prone to glomerular filtration and therefore, to significant renal clearance. To address this and to slow subcutaneous absorption, insulin lispro was modified through covalent bonding of a 20 kilo Dalton polyethylene glycol moiety to form pegylated lispro (LY2605541). This modification of insulin lispro results in a hydrodynamic size that is 4 times that of insulin lispro and has a significantly longer duration of action.[27]

Pharmacokinetics and pharmacodynamics

Preclinical studies demonstrate that pegylated lispro produces a net uptake of glucose by the liver beginning within 30 minutes of administration. This effect is similar to endogenously produced insulin and different from exogenously administered human insulin.[28]

The pharmacokinetics of pegylated lispro were investigated in a trial of 32 patients with T2DM in a 24-hour

euglycemic clamp study.[29] Across dose levels (3-9 nmol/kg), the elimination half-life ranged from 44.7 hours to 75.5 hours, suggesting that pegylated lispro acts as a basal insulin analog with a duration of metabolic action longer than 24 hours. Steady state was reached in 7 to 10 days with a peak-to-trough fluctuation <1.5, indicating a relatively peakless blood level at steady state. As steady state was achieved, there were dose-dependent reductions in the prandial insulin dose; FPG also decreased to 60 to 100 mg/dL across dose levels. No severe or prolonged hypoglycemia was observed, although mild hypoglycemia was the most frequently reported adverse event.

Renal impairment appears to have no effect on the pharmacokinetics of pegylated lispro as no changes in apparent clearance or elimination were observed in patients with varying degrees of renal function.[30] Furthermore, there was no difference in tolerability between healthy subjects and those with renal impairment.

Phase 2 clinical trials

Several clinical trials have compared pegylated lispro with insulin glargine in patients with T1DM or T2DM. In these studies, hypoglycemia was defined as a blood glucose ≤70 mg/dL or signs or symptoms associated with hypoglycemia. Severe hypoglycemia was defined as experiencing signs or symptoms of hypoglycemia with severe neurologic impairment requiring assistance from another person, with recovery after carbohydrate intake, glucagon administration, or intravenous glucose.[31,32]

In patients with T1DM, pegylated lispro has been compared with insulin glargine, both in combination with prandial insulin for 8 weeks and followed by crossover treatment.[31] HbA_{1c} was significantly reduced in patients treated with pegylated lispro compared with those treated with insulin glargine (–0.63% vs –0.48%, respectively; $P < .001$) and FPG was similarly reduced (–47.9 mg/dL vs –19.2 mg/dL, respectively; $P = .017$). Interday variability of FPG was significantly reduced with pegylated lispro compared with insulin glargine (–13.1 mg/dL vs –4.8 mg/dL, respectively; $P < .001$). The rate of hypoglycemic events was higher with pegylated lispro than with insulin glargine (8.74 vs 7.36 events/30 days, respectively; $P = .037$), but lower for nocturnal hypoglycemia (0.88 vs 1.13 events/30 days, respectively; $P = .012$). Over the 8 weeks, the dose of prandial insulin decreased with pegylated lispro (from 0.23 to 0.19 units/kg-day), but increased slightly with insulin glargine (from 0.23 to 0.24 units/kg-day) ($P < .001$). Over 8 weeks, pegylated lispro was associated with weight loss (–1.2 kg), whereas patients treated with insulin glargine gained weight (0.69 kg) ($P < .0001$).

In two 12-week, randomized, open-label studies, there was no difference between pegylated lispro and insulin glargine with respect to either HbA_{1c} reduction (–0.7% vs –0.7%, respectively) or fasting blood glucose reduction (–25.9 mg/dL vs –24.5 mg/dL, respectively).[32,33] However, intraday blood glucose variability was significantly reduced with pegylated lispro compared with insulin glargine (34.4 mg/dL vs 39.1 mg/dL, respectively; $P = .031$); interday variability was similar between groups.[32] In both studies, the rate of nocturnal hypoglycemia was reduced by 48% with pegylated lispro compared with insulin glargine ($P = .021$); the incidence of overall hypoglycemia was similar for each group. The reduction in nocturnal hypoglycemia resulted in a significant reduction in the impact of hypoglycemia on patient behavior and fear of hypoglycemia with pegylated lispro compared with insulin glargine ($P = .026$).[33] With regard to weight, patients treated with pegylated lispro lost 0.6 kg, while patients treated with insulin glargine gained 0.3 kg ($P = .001$).[32] Mean increases in alanine aminotransferase and aspartate aminotransferase were observed in the pegylated lispro group, although the observed mean values remained within the normal range at study end (26.5 and 32.7 units/L, respectively). Two patients had liver enzymes more than 3 times the upper limit of normal with no change in total bilirubin or alkaline phosphatase; further investigation in large, phase 3 trials is needed.

Use of continuous glucose monitoring has also shown that patients with T2DM treated with pegylated lispro compared with insulin glargine experience significantly less glucose variability during the day and at night.[34] In addition, patients treated with pegylated lispro spend less time with interstitial glucose <70 mg/dL during the night compared with those treated with insulin glargine (11 minutes vs 38 minutes, respectively; $P = .024$) and during the 24-hour period (25 minutes vs 83 minutes, respectively; $P < .001$). Fewer patients treated with pegylated lispro experienced any hypoglycemia compared with those treated with insulin glargine (50.0% vs 78.3%, respectively; $P = .036$) and nocturnal hypoglycemia (20.5% vs 47.8%, respectively; $P = .027$).

In summary, pegylated lispro insulin exhibits pharmacokinetic and pharmacodynamic profiles of a basal insulin with a duration of effect longer than 24 hours. Glycemic reductions are significantly greater than (T1DM) or similar to (T2DM) that of insulin glargine. Glucose variability during the day and at nighttime is similar to or less than that of insulin glargine; however, the incidence of nocturnal hypoglycemia with pegylated lispro is significantly less than that of insulin glargine resulting in reduced fear of hypoglycemia with pegylated lispro.[33] Phase 3 clinical trials are under way.

CONCLUSION

Insulin is an important treatment option that has undergone significant evolution in terms of its purity and formulation.

New formulations are expected to become available in the near future that will more closely mimic the actions of physiologic insulin, thereby expanding the role of insulin in treating patients with diabetes. Improvements have also been made in duration of action, blood glucose variability, and safety, particularly regarding reduced hypoglycemia. These offer further opportunities to enhance patient acceptance, convenience, and dosing flexibility, with closer alignment to patient needs. ●

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Effective Utilization of Insulin in Patient Management

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DISCLOSURES
Dr Heile has disclosed that he on the advisory board for Novo Nordisk, Inc. He is on the speakers' bureaus for Bristol-Myers Squibb Company/Amylin Pharmaceuticals, LLC, Janssen Pharmaceuticals, LLC, Novo Nordisk, Inc., and sanofi-aventis U.S. LLC.

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The management of a patient with type 2 diabetes mellitus (T2DM) is typically a long-term process characterized by evolving strategies to meet and maintain the patient's glycemic, cardiovascular, lifestyle, and other goals. Frequent problem solving is needed to individualize treatment based on a patient's needs, interests, beliefs, and capabilities, as these factors will change over time.[1] Life stressors, including health-related financial concerns, must also be addressed as they arise since they may impact a patient's ability to self-manage their T2DM. Patients' preconceived notions about treatment are especially important to consider when initiating or intensifying insulin therapy.

While a recent survey found that more than half of patients with T2DM viewed insulin as having a positive impact on physical well-being, insulin is often associated with negative connotations by both patients and health care providers (HCPs).[2-4] Negative associations on the part of HCPs are generally based on clinical experience, and include fear of hypoglycemia and weight gain, the need for extensive patient education, and anticipation of poor patient adherence.[5,6] Patients' negative associations about insulin often stem from the experiences and perceptions of family members, friends, and in this "connected" world, the Internet and society at large. Consequently, beyond concerns about hypoglycemia and weight gain, patients may see insulin as toxic, potentially promoting or worsening the complications of diabetes. They may view insulin as a mark of personal failure and as hastening adverse outcomes and even death.[7] A feeling held by many patients with T2DM is that of personal responsibility for the need for medications, weight gain, hypoglycemia, and other consequences surrounding their T2DM. HCPs should avoid contributing to these unfavorable perceptions by helping patients recognize the predictable course of T2DM.

Since these negative connotations can have a major impact on the patient's willingness to self-manage their diabetes, it is important to identify and address any misconceptions about insulin—and diabetes management in general—beginning at the time of diagnosis. This article focuses on strategies to facilitate the effective use of insulin therapy in primary care. Case studies are provided to illustrate how these strategies may be employed in the primary care setting.

COMMUNICATION, COLLABORATION, EDUCATION

As a lifelong disease that requires daily lifestyle and pharmacologic intervention, T2DM is largely a self-managed disease. One study estimated that patient-related factors accounted for 95% of the variability leading to improvement in the glycated hemoglobin (HbA_{1c}) level, while provider-related factors accounted for only 5%.[8] In patients whose HbA_{1c} did not improve, provider-related factors had no impact.[8] These results underscore the importance of the patient in the success or failure of their diabetes management and associated health-related outcomes; the results also suggest that without provider influence, improvement in patients' glycemic control is unlikely. As a consequence, working with and supporting the patient with T2DM is a focus of patient management.

Communication

Timely, clear, and courteous communication is of primary importance to patients

with diabetes as it sets the tone and provides the pathway for a collaborative relationship with the provider.[9,10] Effective communication is often difficult to accomplish in the busy primary care setting, with time constraints cited as a common reason for poor communication.

The provider's conversational style is also important.[11,12] Think about the times you and your patient discuss insulin. Does the tone of your voice change? Do you hesitate? Do you present concepts at a level the patient can comprehend? Beyond verbal communication, body language and nonverbal cues are also important. When talking about insulin, does your body language demonstrate caution or fear? Do you project a reluctance to discuss insulin? Do your words invite discussion, but your body language does not? These are all messages your patient will receive and process during the visit; therefore, it is important to offer your patient optimistic phrases and body language that convey a willingness to talk openly.

Collaboration

Patients view their relationship with their provider as integral to engaging more fully in their own care.[9] While good communication and a good relationship between patient and provider are vital to an effective, collaborative relationship, involving the patient in the decision-making process is also essential. In fact, patient self-efficacy is enhanced when the provider acts more as a coach, working *with* the patient to find solutions to problems rather than solving problems *for* the patient.[13]

Effective collaboration can also include the involvement of other HCPs, including nurses, pharmacists, diabetes educators, and medical assistants—all of whom should share the same treatment objectives. As part of a larger diabetes care team, these HCPs can lend their specialized knowledge and skills to help the patient find the best solutions to the challenges in controlling their diabetes. These efforts may improve the patient's role in the self-management of their treatment, increase patient satisfaction with the health care system overall, and reduce the time commitment of the primary care provider (PCP).[14] For patient convenience, it may be advisable for team members to meet with the patient immediately following the visit with the PCP; it should, however, be determined if the patient's insurance will pay for a visit with a nonphysician team member on the same day as the visit with the physician. Recommendations for redesigning the diabetes care team are available from the National Diabetes Education Program. (http://www.ndep.nih.gov/media/NDEP37_RedesignTeamCare_4c_508.pdf).

Communication among patients can also be effective in improving self-management. This may be achieved through shared medical visits, support groups, or a mentoring program. Shared medical visits involve multiple patients meeting together with the physician or other HCPs to discuss diabetes-related issues and to share problem solving tactics.[15,16] Newly diagnosed patients, for example, can meet with patients who have had diabetes for several years, or patients with uncontrolled glycemia can meet with those with good glycemic control. Ideally, patients who serve as mentors should demonstrate good self-efficacy in terms of managing their treatment.

Techniques to foster collaboration and uncover patient concerns

Several techniques have been developed that focus on working with the patient to identify concerns and reach acceptable solutions. These include solution-focused interviewing, motivational interviewing, and the medication interest model.[17-22]

Solution-focused interviewing, which is based on solution-building rather than problem solving, focuses on a patient's desired future rather than on past problems. The provider's role is to guide the discussion to help the patient identify the skills, knowledge, and other resources needed for the patient to achieve their vision of the future.[17]

Motivational interviewing is a process that respects the patient's autonomy while guiding them through a discussion about their diabetes.[18-20] It involves having the clinician ask open-ended questions, providing affirmation to patient responses, employing reflective listening skills, and presenting summary statements. This approach recognizes the fact that patients approach problems with different levels of readiness to institute change. The 4 general principles invoked in motivational interviewing include expressing empathy, which demonstrates an understanding of the challenges faced by the patient with diabetes, and ultimately helps build solidarity with the patient by working together to solve problems related to diabetes treatment. The second principle involves developing disparity with the patient by showing them how their stated goals do not coincide with their current situation. Doing this helps generate motivation for change. Another principle is to "roll with resistance," which recognizes the fact that there is little value in trying to

> Patient self-efficacy is enhanced when the provider acts more as a coach, working *with* the patient to find solutions to problems rather than solving problems *for* the patient.

modify behavior in a patient who is not receptive to change. In this instance, it is preferable to approach a problem with a fresh perspective, or put it aside to explore other challenges. Finally, the PCP should support self-efficacy by making the patient aware of the things that they have the power to change and supporting their transformative actions.

The medication interest model was developed to improve medication adherence.[21,22] This model integrates the principles of motivational and solution-focused interviewing strategies that focus on the "choice triad," an evidence-based set of interviewing techniques that seek to understand how and why patients choose to start or stay on a medication. The "choice triad" is based on the premise that a patient initiates or adheres to a medication because they: (1) believe they have a medical issue for which they want relief; (2) are motivated to try a medication because they believe it may provide relief; and (3) believe the benefits of the medication outweigh its potential risks. The medication interest model provides specific, behavior-oriented interviewing techniques for uncovering patient concerns for each of the 3 choices in the triad and to subsequently address these concerns.

Technological advances

Technological advances related to communication can facilitate improved collaboration. Patient web portals, which integrate the patient's personal and electronic health records, have been shown to enhance patient-provider communication, increase overall patient satisfaction with care, expand patient access to health information, and improve disease management and patient outcomes in diabetes.[23,24] Patient web portals offer several benefits to providers as well, including strengthened collaboration and simplified transmission of patient education. One self-described benefit to providers who collaborated to develop a patient web portal was an enhanced sense of community and renewed focus.[23] Patient web portals that are complex and offer considerable functionality may require patient education regarding their use.[23]

Many of the attitudes and behavioral cues that providers bring to the educational process can either foster acceptance or hinder treatment in patients with diabetes.

Many software applications have also been developed to aid in tracking patients' blood glucose levels, as well as in managing other aspects of diabetes such as dietary habits, carbohydrate counting, and amount of exercise. Examples of some of these can be found through the American Diabetes Association (ADA) (http://forecast.diabetes.org/magazine/features/2012-diabetes-software-apps or http://forecast.diabetes.org/apps-jan2013).

Collaborative programs

Various states and health care delivery systems have formally combined their efforts to improve 1 or more aspects of diabetes prevention or management. In California, for example, patient advocates, health care institutions, industry groups, government agencies, foundations, and other entities have worked together for more than 3 decades to prevent diabetes and its complications. Examples of these collaborative efforts include the following health initiatives:

- **California Diabetes Program**—http://www.caldiabetes.org/
- **The Health Collaborative** (Cincinnati, OH)—http://the-collaborative.org/
- **University of Massachusetts-Memorial Medical Center**—http://www.umassmemorial.org/umass-memorial-health-care/for-providers/diabetes-collaborative-project
- **The Minnesota Diabetes Plan 2015**—http://www.minnesotamedicine.com/PastIssues/PastIssues2011/August2011/TheMinnesotaDiabetesPlan2015.aspx
- **The Montana Diabetes Project (MDP)**—http://www.dphhs.mt.gov/publichealth/diabetes/

Education

The importance of providing education to patients is demonstrated by an analysis of data from the National Health and Nutrition Survey, 2007-2008, which showed that patients were 4 to 8 times more likely to perform a specific diabetes-related self-management behavior (eg, increasing physical activity or losing weight) if recommended to do so by the provider.[23] Similar behaviors were observed from the TRIAD telephone surveys of patients with diabetes in Michigan.[24]

Many of the attitudes and behavioral cues that providers bring to the educational process can either foster acceptance or hinder treatment in patients with diabetes. One technique that was found to be useful in encouraging patient acceptance of a specific treatment is to "work from yes rather than no." In other words, patient acceptance is generally greater if a treatment option is compared with another option that has not worked for the same patient—or has limitations. For example, concerns about self-injecting insulin can be reduced by telling the patient that insulin involves an injection under the skin with a small, fine needle that most patients say causes no pain, in contrast to the intramuscular injections in the arm

with a larger needle that are used for antibiotics or vaccines. Referring to these as "injections" rather than "shots" also causes less patient concern.

As noted earlier, there may be many preconceived notions about diabetes and insulin, so it is important to identify and address these notions as early as possible. Patients should be counseled early in the disease process that T2DM is a predictable disease whose control will likely require the use of insulin at some point in time. Describing T2DM as a "progressive disease" should be avoided, as patients often find this phrase demotivating because of its expectation of inevitability. Patients should understand that while there are therapies that are expected to work well early in the disease, as things change, therapy will need to be intensified to ensure that blood glucose levels remain within the goal range. Restating glycemic and other treatment goals periodically is also recommended since these targets are oftentimes not clear to patients.[25]

Insulin

The management of patients with T2DM taking insulin has evolved a great deal over the past decade. The advent of insulin analogs made it possible to be more efficient in managing patients to targeted glycemic goals with fewer negative effects, such as hypoglycemia, weight gain, and treatment complexity, on their quality of life.

Several approaches to treating patients who are initiating insulin may be utilized. First, inquire about the patient's general level of energy. Many patients who have been hyperglycemic for some time are quite fatigued, and it may be very helpful to let the patient know that as glycemic control is improved, most patients feel a renewed sense of energy. Similarly, many patients report sleep disturbances when their blood glucose levels are high. This can be a direct effect of hyperglycemia, or a result of having to get up many times during the night to urinate. Normalizing the blood glucose level with insulin often improves sleep patterns.

Second, it is important to ask the patient if family members or friends have experience with insulin. Because the attitudes of others often color the patient's own perception of insulin therapy, understanding the patient's viewpoint is important. Some of these perceptions may be based on experience with older bovine and porcine insulins, or neutral protamine Hagedorn (NPH) insulin. If so, patient anxiety can often be minimized by comparing the advantages of currently available insulins with earlier formulations. It is important to emphasize that reductions in adverse events, such as hypoglycemia, weight gain, and allergic reactions, are positive features of newer generations of insulin, in addition to the ease of use of commercially available pen devices. While patients in clinical practice do not commonly express needle phobia, it can be helpful to have the patient self-inject in the office in order to experience, first-hand, the relatively pain-free injections with the smaller needles currently available.

One major objection that patients may have about insulin therapy is the need to take insulin for the rest of their lives. A technique that can be effective in overcoming this objection is to offer insulin therapy as a short-term experiment. Typically, for patients with T2DM, insulin treatment is started as basal insulin, with 1 administration daily. It is, of course, important to explain to the patient the process of using daily insulin and checking blood glucose levels. Inviting patients to telephone or e-mail their blood glucose level results at 1 week and to return in 2 weeks with their blood glucose level log can help send the message that the provider remains engaged in their ongoing care. As part of this short-term experiment, the patient should be assured that if the insulin is intolerable, other treatment options will be discussed. This approach gives the patient permission to undergo a "trial" with the insulin in order to experience the benefits, without a long-term commitment. Using this approach, it is unusual for a patient to discontinue the insulin after experiencing its benefits.

> Identifying and addressing challenges with insulin therapy through individualized patient education is also important.

Various algorithms have been suggested to assist HCPs in initiating or titrating insulin. Here are some examples:

- **California Diabetes Program**—http://www.caldiabetes.org/content.cfm?categoriesID=56&contentID=1274
- **Indian Health Service**—http://www.ihs.gov/MedicalPrograms/Diabetes/index.cfm?module=toolsGCHowToInsulin
- **Texas Department of State Health Services**—http://www.dshs.state.tx.us/diabetes/pdf/toolkit/appendix.pdf

In summary, insulin is an important treatment option for patients with T2DM requiring extensive support by the PCP and diabetes care team. To provide this support, effective communication and a collaborative relationship that stimulate patient involvement and motivation are essential. Identifying and addressing challenges with insulin therapy through individualized patient education is also important. Strategies to provide this support in the primary care setting are described in the following case studies.

THREE CASE STUDIES

CASE STUDY 1 ▶
Ralph (insulin resistance; addition of prandial insulin; adherence)

Ralph is a 63-year-old African American male who is a soon-to-be retired carpenter. Diagnosed with T2DM 12 years ago, he has attended clinic for many years. He was initially treated with oral agents, but his blood glucose did not respond well. The addition and titration of insulin glargine to 65 units twice daily has not resulted in much improvement, as his HbA_{1c} has been consistently >8.0%. His most recent HbA_{1c} was 9.4%. Ralph reports taking his oral medication regularly, but admits he forgets his morning dose of insulin glargine 2 to 3 times a month. He denies undergoing regular exercise, but reports that he has remained active at work. He also reports that his wife is in charge of his diet at home; however, he does eat fast food for lunch every day on the job site, with frequent unhealthy snacks due to hunger.

Current medications

- Metformin 1000 mg twice daily
- Glimepiride 4 mg once daily
- Insulin glargine 65 units at breakfast and dinner
- Lisinopril 20 mg once daily
- Amlodipine 5 mg once daily
- Atorvastatin 40 mg once daily
- Aspirin 81 mg once daily

Physical examination

- Blood pressure (BP): 128/78 mm Hg
- Weight: 280 lb
- Body mass index (BMI): 36 kg/m^2
- General: Obese African American male with no obvious distress at this time
- Feet: Skin intact, pulses positive, bilateral hallux valgus and hammertoe deformity. 10 g Semme-Weinstein Monofilament and 128 Hz tuning fork sensation are intact
- Eyes: No obvious retinopathy. He is referred for an eye examination
- Cardiovascular: Intact with established hypertension and hyperlipidemia

Blood glucose levels

A review of the blood glucose log for the 2 months prior to the follow-up visit shows numerous blood glucose levels >200 mg/dL. As all were recorded in the morning, it is presumed that these were fasting blood glucose levels.

Clinical impression

This is a 63-year-old patient who is mostly adherent with his medications, but has significant adherence difficulties with the diet and exercise aspects of his treatment plan. He is taking a significant dose of insulin to have his blood glucose remain elevated (insulin glargine dose of 1.02 units/kg/d).

Challenges and concerns

Ralph is resistant to change and provides contradicting reasons for not wanting to make any changes. He states that because things have worked well so far, why change them? At the same time, he states frankly that the changes that have been made in his medications have not worked so far. He does not like to stick his finger "just to get bad news." He does not like taking insulin as he does not see it as working for him. ("Look at my blood sugars, do you think it is working?") Ralph does not do any self-management at work. He reports being embarrassed by having diabetes, and that in his family, diabetes was not discussed as it was seen as a weakness. He states that he works with a "tough bunch of guys" and does not want to feel limited by his diabetes.

Physician response

- Explain the natural progression of T2DM. While medications may have worked in the past, intensification of treatment is needed to maintain glycemic control
- Focus on the things he is doing correctly. Ask him to think of situations in the past where he has had to implement change. Ask him to describe how he motivated himself to make these changes
- Explain that the purpose of blood glucose monitoring is not to be a negative reminder of his diabetes, but rather a tool that allows us to track and trend the management
- Discuss his impression that diabetes is a weakness. Explain that diabetes should be looked at no more negatively than hypertension or arthritis, and that diabetes requires ongoing attention, including adjustments in lifestyle and diet. Explain that good management of his diabetes can be looked at as a personal achievement
- Encourage Ralph to talk about his family's response to diabetes as this needs to be addressed and resolved before meaningful improvement will be made

Treatment plan

- Refer Ralph to the certified diabetes educator (CDE) and engage him in a diabetes self-management program
- Begin monitoring blood glucose levels 3 to 4 times daily at different times to establish a trend
- Discuss exercise activity and help Ralph make a plan
- Ask Ralph to log his food intake for the next 2 weeks
- Ask Ralph to return in 2 weeks for follow-up

Follow-up visit 2 weeks later

Ralph continues insulin glargine 65 units at breakfast and dinner, metformin 1000 mg twice daily, and glimepiride 4 mg once daily. He visited with the CDE and has agreed to take a walk with his wife after dinner and to bring his lunch and snacks from home.

Clinical impression

Ralph is reasonably adherent with his medications and he checks his blood glucose enough to analyze trends. Review of his blood glucose log shows that his morning blood glucose ranges from 152 to 206 mg/dL, and his pre-lunch and dinner blood glucose ranges from 180 mg/dL to 308 mg/dL. While his fasting blood glucose levels are some of the best levels during the day, they are still not at goal. He demonstrates considerable postprandial hyperglycemia and has no identified episodes of hypoglycemia.

Ralph will require the addition of prandial insulin to better control his blood glucose. There are several things to consider when initiating prandial insulin in the presence of basal insulin and oral glucose-lowering medications. If there are episodes of nocturnal hypoglycemia or the fasting blood glucose levels are close to goal, it is prudent to reduce the total daily dose of basal insulin when introducing prandial insulin. In Ralph's case, all of the measured blood sugars are above goal, so reducing the dose of basal insulin will likely result in higher blood glucose levels. Continuing oral medications, particularly metformin, is often beneficial, although continuing the secretagogues, such as glimepiride, when initiating prandial insulin, is more controversial.

Treatment plan

- Reduce glimepiride to 2 mg once daily
- Begin insulin aspart 0.1 units/kg (12 units) before each consistent carbohydrate meal
- Ask Ralph to monitor his blood glucose level 4 times a day and when symptoms of hypoglycemia are experienced
- Continue metformin 1000 mg twice daily, insulin glargine 65 units twice daily
- Refer to CDE to reinforce insulin technique and recommend lifestyle interventions
- Ask Ralph to return in 2 weeks for follow-up

Follow-up visit 2 weeks later

Ralph returns stating that he is doing okay with the basal-bolus insulin regimen. He has visited with the CDE and has learned how to moderate his food intake by measuring his portions of carbohydrate. He has also learned to distinguish between carbohydrates, fats, and proteins in food. He states that he has been noticing some low blood glucose levels, which he finds frustrating. He presents with the blood glucose log shown in **TABLE 1**.

Clinical impression and plan

Ralph's blood glucose pattern is somewhat typical of a

TABLE 1 **Ralph: follow-up blood glucose log (mg/dL)**

Date	Breakfast	Lunch	Supper	Bedtime	Overnight
3/1/2013	131	112	121	146	
3/2/2013	125		136	154	
3/3/2013	138	76	234	176	
3/4/2013	122	134	142	122	
3/5/2013	141				
3/6/2013	133	66	78	187	
3/7/2013	145				
3/8/2013	129	144	153	160	106
3/9/2013	132				
3/10/2013	123	62	208	165	
3/11/2013	122				
3/12/2013	143	58	94	134	122
3/13/2013	116	144	149	128	
3/14/2013	136	83	112	153	

patient who remains on the sulfonylurea after the prandial insulin is initiated. This was discussed, and it was decided to discontinue glimepiride. This should resolve his occasional low blood glucose at lunch and supper. If it does not, Ralph should be instructed about lowering the dose of insulin aspart around times of higher activity levels or exercise. The insulin aspart has reduced the late day and evening hyperglycemia. Congratulating Ralph for improving his medication adherence and intensifying his lifestyle management is important to sustain his motivation. It was agreed that Ralph would telephone in 1 week to report his blood glucose levels to allow for adjustment of his insulin doses following discontinuation of the glimepiride. He will follow up with the CDE in 1 month. Follow-up with the physician was scheduled to coincide with his next HbA_{1c} measurement.

CASE STUDY 2 ▶
Dan (frequent hypoglycemia with NPH insulin)

Dan is a 58-year-old Caucasian male who has had T2DM for more than 20 years. A new patient to you, his ophthalmologist reports that he has diabetic retinopathy and may require laser surgery in the near future.

He tests his blood glucose level early in the morning and infrequently before bed. He complains of lower extremity edema, weight gain, and labile blood glucose levels, especially overnight. He frequently has unexplained low/high blood glucose levels in the early morning that are not related to what he ate the night before. This causes Dan to be concerned about hypoglycemia, especially overnight. He reports that he could eat healthier and that he does not count the carbohydrate content of his meals. He also reports wide variability in the carbohydrate and caloric content of lunch and dinner due to his work as a salesman, as part of which he frequently takes clients out for meals. He usually goes to bed late, although he occasionally goes to bed early and misses his bedtime snack, especially on weekends. He requests advice on how to gain better control of his diabetes.

Current medications

- NPH insulin 25 units twice daily at breakfast and bedtime
- Regular human insulin 15 units prior to breakfast and dinner
- Metformin 1000 mg twice daily
- Pioglitazone 30 mg once daily
- Enalapril 10 mg twice daily
- Candesartan 16 mg once daily
- Aspirin 81 mg once daily

Physical examination

- BP: 126/74 mm Hg
- Weight: 193 lb
- BMI: 26 kg/m^2
- General: Well-appearing male
- Feet: Skin intact, sensation intact
- Cardiovascular: Intact with established hypertension

Laboratory

- HbA_{1c}: 8.1%

Clinical impression

Human insulins have much higher coefficients of variability (see *Overview of Current Insulin Formulations* in this supplement) compared with analog insulins and are more likely to cause unpredictable blood glucose levels despite consistent eating patterns. Dan's diet is much too spontaneous and unpredictable to be successful with fixed dosing insulin.

Thiazolidinediones and multiple daily dosing of insulin frequently cause weight gain and peripheral edema. His early morning labile blood glucose and occasional hypoglycemia overnight are likely due not only to the variability in the peak and duration of effect of the NPH insulin given at dinner, but also the duration of action of the regular human insulin given at dinner extending into his sleep time. Missing snacks at bedtime on weekends may also contribute to nocturnal hypoglycemia. Labile morning blood sugars can be caused by occasional rebound hyperglycemia following overnight hypoglycemia or overcorrection of nocturnal hypoglycemia with carbohydrates.

Switching from NPH insulin to either insulin detemir or insulin glargine should be helpful in resolving these issues. It is advisable to reduce the total daily dose by 20%, particularly if NPH insulin was administered twice daily and insulin detemir or insulin glargine are to be administered once daily in the evening. The dose of the insulin detemir or insulin glargine can then be titrated based on daily monitoring of the fasting blood glucose. Finally, secondary prevention of progression of his diabetic retinopathy depends on aggressive, but safe, reduction of his HbA_{1c} to <6.5%.

Patient barriers and concerns

Fluctuations in Dan's eating and sleep habits make control of his diabetes challenging. This is further complicated by his inability to accurately count the carbohydrate content of meals. On the other hand, he appears motivated to make changes to better control his diabetes, but is concerned about hypoglycemia.

Physician response

- Acknowledge Dan's motivation to better control his diabetes
- Explain that intensifying his management is urgently

needed to slow the progression and complications of his diabetes
- Explain that his eating and sleep habits make control of his diabetes challenging
- Discuss possible strategies to improve his lifestyle management and determine what changes Dan is willing to make
- Investigate possible unrecognized signs and symptoms of hypoglycemia; provide education

Treatment plan

- Discontinue pioglitazone, but continue metformin
- Discontinue both NPH and regular human insulin
- Start insulin detemir 40 units at bedtime
- Start insulin aspart 1 unit for every 10 g of carbohydrate (meal bolus) and 1 unit for every 25 mg/dL above his target blood glucose of 120 mg/dL before meals and at bedtime (correction bolus)
- Ask Dan to monitor his blood glucose level 4 times a day and when symptoms of hypoglycemia are experienced
- Refer to local dietitian or CDE for carbohydrate counting training
- Invite for a follow-up visit in 2 months

At this visit, Dan met with the office nurse who provided education regarding both the FlexPen and self-titration based on the average of the fasting plasma glucose (FPG) over 3 days. Dan was also introduced to the concept of proportions and the fact that he would need approximately 50% of his insulin as basal (insulin detemir) and the other 50% as bolus (insulin aspart) for meals and high blood glucose levels. He was provided a brief overview of how to choose healthy, low carbohydrate entrees when eating out. The patient was provided references for smart phone apps like "Calorie King" for carbohydrate counting (http://www.calorieking.com/mobile/about/). If he is unable to do this, it was recommended that he eat healthy store-bought meals that have carbohydrate counts on the package.

Dan was also provided information about supplemental prandial insulin and how the correction factor is calculated. The correction factor estimates the fall in blood glucose per unit of rapid- or short-acting insulin.[26] As noted above, a correction factor of 25 mg/dL has been empirically set for the correction bolus of insulin aspart. To calculate the actual correction factor for the correction bolus, 1500 is divided by the total daily dose of insulin. Since Dan was using a total of 80 units of insulin per day (NPH insulin 25 units twice daily and regular human insulin 15 units twice daily), his correction factor for the correction bolus would be 19 mg/dL per unit of analog insulin (1500 ÷ 80 units ≈19 mg/dL). To make it a safer place to start and easier for Dan to remember, his correction factor could be rounded to 20 or 25 mg/dL. Since Dan's premeal target is 120 mg/dL, he would add 1 unit of insulin aspart to his meal bolus for every 20 mg/dL increment above 120 mg/dL. This should result in his postprandial blood glucose level being within the target <180 mg/dL. The dose of insulin aspart to be administered at mealtime (meal bolus) is calculated by dividing 500 by the total daily dose of insulin (500 ÷ 80 units ≈ 6). This represents the amount of carbohydrate (in grams) disposed of per unit of insulin. In Dan's case, the ratio of 1 unit of insulin per 6 g carbohydrate is quite low initially; a ratio of 1 unit of insulin per 10 g of carbohydrate is easier to remember and a safer place to start (to avoid hypoglycemia) until he is more comfortable with carbohydrate counting. In either case, titration based on frequent blood glucose monitoring is essential.

Follow-up visit 2 months later

The current dose of insulin detemir is now 45 units at bedtime. Review of his before meals and bedtime glucose log reveals his morning blood glucose ranges from 72 to 153 mg/dL (average approximately 120 mg/dL). Premeal blood glucose ranges from 160 mg/dL to 193 mg/dL. His current HbA_{1c} is 7.3%. Dan is much happier that his insulin suits his lifestyle better. His overnight and morning blood glucose levels are more predictable and he feels more confident about recognizing hypoglycemia. He has gained only 1 pound in the last 2 months. He did meet with the dietitian and has downloaded resources to help him with carbohydrate counting.

Clinical impression

Weight gain with improved glycemic control is commonly observed with insulin likely as a result of less glycosuria. The weight gain Dan experienced was small, probably because discontinuation of his pioglitazone and resolution of his edema offset the weight gain associated with insulin. Although his morning blood glucose is within the target of 70 to 130 mg/dL established by the ADA, his premeal blood glucose levels are high. It is likely that his 2-hour postprandial blood glucose levels are not below the ADA target <180 mg/dL needed to lower his HbA_{1c} to <7.0% or the target <140 mg/dL established by the American Association of Clinical Endocrinologists to achieve an HbA_{1c} < 6.5%. While an HbA_{1c} target of <6.5 to 7.0% is needed for Dan to stop the progression of retinopathy, this goal is not suitable for all patients and should be individualized based on patient age and history.

Treatment plan

- Increase insulin aspart to 1 unit for every 8 g of carbohydrate and 1 unit for every 20 mg/dL above his target blood sugar of 120 mg/dL before meals and at bedtime
- Continue metformin and insulin detemir

Dan met with the office nurse who reinforced strategies regarding a healthy diet. They also discussed how to adjust his meal and correction insulin aspart doses and monitor his blood glucose before or after exercise or increased physical activity. Dan was also educated about the need for free carbohydrates (no insulin aspart) to fuel exercise when his blood glucose is in the target range.

CASE STUDY 3▶
Pauline (missed doses/high blood glucose; referral)

Pauline is a 62-year-old female diagnosed with T2DM 12 years ago. Initial management consisting of lifestyle modifications was only moderately successful over 2 years. Subsequent treatment with metformin lowered her HbA_{1c}, but never to <8%. Pauline was then treated with various oral medications and eventually, basal insulin. She has been on insulin detemir for 2 years now and has been receiving 55 units per day for the past 6 months.

Pauline presents today after a 13-month absence from the clinic with complaints of fatigue and painful feet. She forgot her meter, but reports that her blood glucose is rarely below 200 mg/dL. Her blood glucose reached 420 mg/dL after a visit with friends to the "all you can eat" buffet. Pauline claims that she has been adherent with her medications, although her refills ran out several months ago. She states that she almost always takes her evening insulin dose, but that she has significant difficulty with her diet. She denies any meaningful exercise.

Current medications

- Metformin 1000 mg twice daily
- Glimepiride 4 mg once daily
- Pioglitazone 30 mg once daily
- Insulin detemir 55 units at bedtime
- Simvastatin 20 mg once daily
- Olmesartan 20 mg once daily
- Aspirin 81 mg once daily

Physical examination

- BP: 120/78 mm Hg
- Pulse: 76 beats per minute
- Weight: 330 lb
- BMI: 46 kg/m^2
- General: Well-developed obese female
- Eyes: Extraocular muscles intact, no obvious retinopathy (referred for dilated eye examination)
- Cardiovascular: Regular rate and rhythm with good distal pulses; no edema noted
- Feet: Skin intact, pulses positive, 10 g Semme-Weinstein Monofilament and 128 Hz tuning fork sensation are deficient in the distal foot.

Blood glucose levels

- Absent at this visit.

Laboratory

- HbA_{1c}: 11.6%
- Comprehensive chemistry panel, urine microalbumin, lipid panel, and thyroid stimulating hormone—all pending.

Clinical impression

Pauline is a 62-year-old obese female who is marginally adherent to therapy. She has uncontrolled T2DM, diabetic polyneuropathy, hypertension, and hyperlipidemia. Her fatigue is likely secondary to glucose toxicity and sedentary lifestyle; hypothyroidism is being investigated.

Patient barriers and concerns

Pauline is frustrated with her diabetes and sees it as an impediment to her lifestyle. She enjoys her friends and they like to eat. She stopped monitoring her blood glucose because she felt like a failure. She states that she has done okay with her diabetes so far and she does not think the complications will affect her, or if they do, it will be near the end of her life. She does want to regain some of her energy and would like some help with the pain in her feet.

Physician response

- Voice understanding regarding spending time with her friends
- Begin making the connection between continued enjoyment in her activities and better control of the diabetes
- Explain that the pain in her feet is likely a direct result of nerve damage from uncontrolled diabetes
- Ask her what she is willing to change to achieve her goals of being with her friends
- Assure her that changes can be made to her treatment plan, but that she controls her diabetes management

Treatment plan

- Refer to the CDE for comprehensive review of her diabetes self-management education
- Ask Pauline to monitor her blood glucose 3 to 4 times daily at different times and bring her meter to the next visit
- Refill current medications for 1 month and emphasize the importance of adherence
- Ask Pauline to return to the clinic in 2 weeks

TABLE 2 Pauline: first follow-up blood glucose log (mg/dL)

Date	Breakfast	Lunch	Supper	Bedtime	Overnight
3/18/13	244		294	343	
3/19/13	280	320	401	356	
3/20/13	313	330	365	310	
3/21/13	269		404	383	235
3/22/13	301	335		285	
3/23/13	290	259	355		
2/24/13	255			330	
3/25/13			345	385	
3/26/13	275				
3/27/13	313		294	365	212
3/28/13					
3/29/13	273		345	374	
3/30/13					
3/31/13	289		365		

Follow-up visit 2 weeks later

Pauline returns stating that she visited with the CDE. Several lifestyle management changes were discussed; Pauline agreed to take a walk at lunchtime. Pauline continues to complain of her feet hurting. She reports that she is taking her medications better since the last visit. She reports starting to become a bit frightened of her diabetes since her visit 2 weeks ago. Pauline presents her blood glucose log from the previous 2 weeks (**TABLE 2**). She wants to do more, but is unsure of the next steps.

Laboratory

- Comprehensive chemistry panel is normal with the following exceptions:
  - creatinine 1.2 mg/dL
  - sodium 122 mg/dL, glucose (random) 330 mg/dL
  - estimated creatinine clearance 49 mL/min
- Albumin, urine 55 mg/g creatinine
- Thyroid stimulating hormone 1.45 micro units/mL

Physician response

Her PCP is encouraged that Pauline is more engaged with therapy, but is concerned with the blood glucose levels. The PCP is willing to titrate the insulin detemir, but is unsure how to advance the insulin if basal-bolus insulin is required or if it is necessary to split the dose of basal insulin. The PCP is also unsure how to adjust the oral medications in conjunction with insulin. The PCP discusses these concerns with Pauline and they agree that Pauline should be referred to a local endocrinologist (or diabetologist).

Treatment plan

- Consider twice-daily insulin detemir; increase to 60 units at bedtime now pending consultant's recommendation
- Continue metformin, glimepiride, pioglitazone
- Start pregabalin 50 mg twice daily for neuropathic foot pain
- Continue checking blood glucose levels
- PCP to call diabetes specialist to discuss case and refer

Discussion

There are many situations in which the PCP may consider referral to an endocrinologist or diabetologist for evaluation and management of a patient. As with Pauline, a patient's treatment regimen can become quite complex when the dose of basal insulin continues to increase and split doses may be needed, or basal-bolus therapy is contemplated and the patient is taking oral medications.

Other situations where referral to a diabetes specialist is encouraged include the following:

- Concomitant treatment with a medication that interferes with control of the diabetes, such as ongoing systemic steroid therapy, certain psychiatric medications (such as atypical antipsychotics), and chemotherapy medications that cause nausea/vomiting; changes in eating patterns; or the stress of chronic illness
- Severe hyperglycemia and recent diagnosis of diabetes
- Recurrent or severe hypoglycemia, especially when it requires management in the emergency department or hospital

TABLE 3 Pauline: second follow-up blood glucose log (mg/dL)

Date	Breakfast	Lunch	Supper	Bedtime	Overnight
4/16/13	234		276	348	
4/17/13	264	318	414	344	
4/18/13	295	328	373	311	
4/19/13	303		410	381	243
4/20/13	304	334		281	
4/21/13	289	264	351		
4/22/13	248			298	
4/23/13			346	384	
4/24/13	276				234
4/25/13	310		302	371	
4/26/13					
4/27/13	282		333	338	
4/28/13					
4/29/13	250				

- Pregnancy, since the tight blood glucose control that is necessary to manage a pregnancy is difficult. In addition, the selection of glucose-lowering therapy needs to be considered in light of the developing fetus and maternal health
- Patients considering insulin pump therapy
- Treatment with large doses of insulin or regular human insulin U-500
- Patients with significant emotional or psychiatric challenges

Endocrinologist/diabetologist visit

Pauline was able to visit with the diabetes specialist within a month. The diabetes specialist conducted a thorough history and physical examination and reviewed Pauline's health record and blood glucose log (**TABLE 3**).

Patient barriers and concerns

Pauline reported that her foot pain has eased since starting pregabalin and she is now walking 15 minutes at lunch time. She remains concerned about her foot pain and her diabetes in general, but enjoys the time spent with friends.

Diabetologist response

- Assure Pauline that more can be done, but that this will require a higher dose of basal insulin, as well as the addition of prandial insulin to control the postprandial hyperglycemia
- Encourage Pauline by stating that proper treatment will slow disease progression and complications and that she will feel better, just as her foot pain has eased with pregabalin
- Discuss with Pauline the importance of lifestyle changes, especially as it relates to time spent with friends. Determine if Pauline is willing to consider changes. If so, refer to CDE for further discussion about strategies
- Discuss simplifying Pauline's treatment plan by discontinuing glimepiride and pioglitazone

Treatment plan

- Discontinue glimepiride, pioglitazone
- Continue metformin 1000 mg twice daily
- Split the insulin detemir dose to 33 units before breakfast and 33 units at dinner.
- Initiate insulin lispro 10 units before each meal
- Refer to CDE for follow-up regarding basal-bolus therapy, proper injection technique, hypoglycemia awareness, and strategies to reduce food as a focus during time spent with friends
- Invite for a follow-up visit in 1 month

CONCLUSION

Insulin is an important treatment option for patients with T2DM that is often associated with several challenges. Advancements in insulin formulations and delivery systems have reduced challenges, such as hypoglycemia, weight gain, and ease of administration. Effective communication and a collaborative relationship between patient and

provider can identify and address, through individualized patient education, the variety of challenges associated with insulin therapy. ●

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