ABSTRACT: Great improvements have been made to insulin preparations over the years, including the development of insulin analogs, which were designed to overcome the disadvantages of traditional human insulins in the treatment of type 1 and type 2 diabetes. Insulin analogs more closely mimic the physiological insulin profile and are therefore associated with an improved balance between glycemic control and tolerability. They are also associated with a lower risk of hypoglycemia, less weight gain, and greater treatment flexibility than human insulins. These benefits, in combination with new insulin delivery devices, such as pens, have greatly improved patients’ treatment satisfaction and medication adherence, leading to improvements in clinical outcome. This article reviews the advantages of insulin analogs over human insulin for the treatment of type 1 and type 2 diabetes.

Insulin was first used to treat diabetes in the 1920s. Early advances in therapy consisted of improvements in the purification and modification of pharmaceutical formulations in order to extend their duration of action. The addition of protamine reduced the solubility of insulin at physiological pH, slowing down its absorption after subcutaneous injection and thereby prolonging its action. In 1935, Scott and Fisher further demonstrated that the addition of zinc to insulin prolonged its action profile. Neutral protamine hagedorn (NPH), developed in the 1940s, was the first intermediate-acting insulin containing equal amounts of insulin, zinc, and protamine.

In the early 1980s, recombinant DNA technology enabled the synthesis of human insulin. However, the suboptimal pharmacokinetic and pharmacodynamic characteristics of human insulin, particularly its natural tendency to form absorption-delaying hexamers, prompted further improvements in the insulin molecule. Recent advances in molecular biology have enabled us to modify the insulin molecule, resulting in analogs with pharmacokinetic and pharmacodynamic properties that more closely resemble those of endogenous insulin in healthy persons. Rapid-acting analogs, such as insulin aspart, insulin lispro, and insulin glulisine, are typically used as mealtime insulin replacement because they mimic the physiological insulin response to food intake (Figure). These analogs, which provide a faster onset and a shorter duration of action than human insulin, are administered immediately before meals and reduce the risk of hypoglycemia in the intervals between meals that is often seen with human insulin.

Traditional basal (long-acting) insulins such as NPH have suboptimal pharmacodynamic profiles, making them an inadequate replacement for endogenous insulin. After injection, basal insulins exhibit a peak concentration and action followed by waning; they have been associated with significant within-subject absorption variability.

The drawbacks of traditional basal insulins prompted the development of long-acting insulin analogs...
such as insulin glargine and insulin detemir, which more closely approximate the natural, constant physiological release of insulin (see Figure). \(^3,5\) Insulin glargine is injected as a solution, but precipitates upon injection into subcutaneous tissue, delaying absorption. \(^8,9\) Insulin detemir, on the other hand, forms hexamers and reversibly binds to albumin, prolonging its absorption and bioavailability. \(^10\)

The need for convenient, effective, and simultaneous supplementation of both prandial and basal insulin with a limited number of injections prompted the development of premixed insulin analogs, \(^3,5\) which are a mixed suspension of a rapid-acting and basal insulin, exposing patients to a lower risk of complications, than less intensive therapy. \(^11\)

Rapid-acting insulin analogs have also been associated with greater reductions in hemoglobin A\(_{1c}\) (HbA\(_{1c}\)) compared with human insulin. In a randomized, open-label, 6-month trial of 1070 patients with type 1 diabetes, Home and colleagues \(^12\) reported that HbA\(_{1c}\) levels were significantly reduced with insulin aspart compared with human insulin (treatment difference, 0.12%; \(P < .02\)). However, the rapid-acting analog combined with basal insulin in this study did not reduce HbA\(_{1c}\) levels as much as expected. This may have resulted from underuse because of patients’ fear of hypoglycemia and investigators’ insufficient experience in insulin aspart dosing. Use of shorter-acting prandial insulin necessitated higher doses of basal insulin, exposing patients to high variability in absorption and the potential for nocturnal hypoglycemia. This risk may undermine rapid-acting analogs’ advantage of greater reductions in HbA\(_{1c}\) levels and could lead to inadequate glycemic control.

Both insulin aspart and insulin lispro have also demonstrated greater postprandial glucose (PPG) control than regular human insulin. \(^12,13\) Insulin aspart plus NPH insulin resulted in significantly lower PPG levels than human insulin plus NPH insulin (Table 1). \(^12\) Similar PPG levels were observed when insulin aspart and human insulin were compared in a randomized, open-label, 6-month study with a 6-month extension period in patients with type 1 diabetes (see Table 1). \(^14\) Importantly, improved PPG control has been associated with a reduced risk of long-term cardiovascular complications. \(^15\)

The high risk of hypoglycemia associated with insulin therapy is one of the major concerns in type 1 diabetes. \(^16\) The development of insulin analogs has reduced this risk in patients with type 1 diabetes compared with human insulins. \(^3\) Home and associates \(^12\) reported significantly fewer major nocturnal hypoglycemic events for insulin aspart than for human insulin (8% and 11% of patients, respectively, experienced major hypoglycemia; \(P < .05\)).

Better overall glycemic control has been achieved with long-acting insulin analogs than with NPH insulin. \(^5\) Many trials have shown that
basal insulin analogs improve the balance between glycemic control and tolerability when compared with NPH insulin.12 In short, at equivalent glycemic control, the incidence of nocturnal hypoglycemia is typically reduced by 30% from baseline to end of trial for insulin analogs when compared with NPH insulin.13

The potential advantages of insulin analogs are best evaluated by comparing all-analog regimens to all-human insulin regimens, because the advantages of each component of the analog regimen are optimized when used in tandem. Greater improvement in glycemic control has been achieved with basal-bolus therapy using insulin analogs compared with an all-human insulin regimen.14,15 Glycemic control was also shown to improve significantly more with insulin detemir/insulin aspart versus NPH/human insulin in an 18-week, randomized, open-label study of 595 patients with type 1 diabetes (HbA1c 7.88% vs 8.11%; P < .001).16

Insulin detemir/insulin aspart improved glycemic control without concomitant weight gain compared with NPH/human insulin.17 Body weight was 1 kg lower at study end with insulin detemir/insulin aspart than with NPH/human insulin (P < .001). The combination of insulin detemir plus insulin aspart also resulted in a lower risk of overall and nocturnal hypoglycemia than NPH/human insulin (21% [P = .036] and 55% [P < .001], respectively).18

In a 32-week, 2-way crossover study of 56 patients with type 1 diabetes, significantly lower HbA1c levels were demonstrated with insulin glargine/insulin lispro than with NPH/human insulin (7.5% vs 8.0%; P < .001).19 Insulin glargine/insulin lispro also reduced the rate of nocturnal hypoglycemia by 44% compared with NPH/human insulin (P < .001).20

**Type 2 diabetes.** Many patients with type 2 diabetes could benefit greatly from insulin therapy. However, physicians and patients alike are often reluctant to initiate insulin therapy, so that insulin regimens may not be started until after oral antidiabetic drugs (OADs) have failed. Delaying insulin initiation has been linked to patients’ lack of awareness of disease progression, aversion to injection, and patients’ and physicians’ concerns about hypoglycemia and weight gain.21,22 Yet several clinical trials have demonstrated a lower risk of hypoglycemia and less weight gain for insulin analogs compared with traditional insulins.16

To initiate insulin treatment, long-acting analogs can be used in a simple regimen (generally once daily) in addition to oral therapy. In studies of insulin-naive patients with type 2 diabetes, use of basal analogs has been associated with significant improvements in glycemic control and with a lower risk of hypoglycemia compared with NPH insulin.17

Aggressive titration of basal analogs has generally resulted in mean HbA1c level decreases of about 1.5%,17 meaning that guideline-recommended HbA1c targets (< 7.0%) are achievable if HbA1c is not already in excess of 8.5%. For example, in a 26-week, randomized, parallel, treat-to-target trial of 476 insulin-naive patients with type 2 diabetes who were inadequately controlled with OADs, the majority of patients (70%) achieved HbA1c target levels of 7.0% or less with insulin detemir and NPH insulin. However, a significantly greater proportion of patients in the detemir group achieved these targets without hypoglycemia during the last 12 weeks of treatment (26% vs 16%, P < .01).23 Patients receiving insulin detemir also achieved HbA1c targets with significantly less weight gain than those receiving NPH insulin (1.2 kg vs 2.8 kg, respectively; P < .001).22

Similar results were observed in a treat-to-target trial of 756 overweight patients with type 2 diabetes inadequately controlled with OAD therapy.24 With the addition of once-daily insulin glargine or NPH insulin to existing OAD therapy, about 60% of patients achieved HbA1c targets of 7.0% or less, and significantly more patients in the glargine group versus the NPH insulin group attained these targets without nocturnal hypoglycemia (33% vs 27%, respectively; P < .05).25

Three different insulin analog regimens were compared in the Treat-to-Target in Type Two (4-T) study, which included 708 patients with type 2 diabetes inadequately controlled with OADs.26 Patients were randomized to receive twice-daily biphasic insulin aspart, 3-times daily

<table>
<thead>
<tr>
<th>Table 1 – Comparison of postprandial glucose levels after main meals following administration of insulin aspart plus NPH or human insulin plus NPH</th>
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<tbody>
<tr>
<td><strong>Postprandial glucose (mg/dL)</strong></td>
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<tr>
<td><strong>After breakfast</strong></td>
</tr>
<tr>
<td><strong>Insulin aspart</strong></td>
</tr>
<tr>
<td><strong>Home</strong>12</td>
</tr>
<tr>
<td><strong>Raskin</strong>14</td>
</tr>
</tbody>
</table>

NPH, neutral protamine hagedorn.

<sup>4</sup> P < .001, <sup>5</sup> P < .01, <sup>6</sup> P < .05.
prandial insulin aspart, or once-daily basal insulin detemir. At 1 year (the first phase of the 3-year trial), the 3 analog regimens were associated with clinically relevant and sustainable reductions in HbA1c. Premixed and rapid-acting analog regimens lowered HbA1c to a similar extent (−1.3% and −1.4%, respectively), but significantly more than the basal insulin regimen (−0.8%; P < .001 for both comparisons). However, patients treated with the premixed and rapid-acting insulin analog regimens had a greater risk of hypoglycemia (5.7 and 12.0 events/patient-year, respectively, vs 2.3 events/patient-year; P = .04) and weight gain (4.7 kg and 5.7 kg, respectively, vs 1.9 kg; P < .001) than those who received the basal regimen. Basal insulin therefore appears to be the most tolerable insulin initiation regimen, though intensification may be necessary over time.

As the disease progresses, patients with type 2 diabetes will eventually need to supplement both basal and prandial insulin. Premixed insulins can be prescribed once or twice daily for insulin intensification when a basal insulin regimen has become inadequate. As Garber and colleagues noted, premixed insulin analogs have several advantages over premixed human insulins. Although both have demonstrated similar HbA1c control (with −60% to 70% of patients achieving HbA1c < 7.0%) and similar rates of minor hypoglycemia (−60% of patients), a lower risk of major hypoglycemia was seen for premixed analogs compared with premixed human insulin (0% to 5% vs 10% to 15% of patients, respectively).

Lower FPG levels have also been observed for premixed insulin analogs versus premixed human insulins. For example, postprandial control was significantly greater for BIAsp 70/30 when compared with biphasic human insulin 30 (BHI 30) and lispro mix 75/25 (17% [P < .001] and 10% [P < .05] lower postprandial blood glucose values, respectively) in a randomized, open-label, single-dose, 3-way crossover trial of 61 patients with type 2 diabetes. However, within-subject variability of fasting blood glucose and weight gain was significantly lower with insulin detemir than with NPH insulin.

An all-analog regimen (insulin detemir plus insulin aspart) showed similar glycemic control when compared with an all-human insulin regimen (NPH insulin plus regular human insulin) in 395 patients with type 2 diabetes treated for 22 weeks in an open-label, randomized trial, but insulin detemir/insulin aspart treatment resulted in significantly lower within-person daily glucose variation and significantly less weight gain (see Table 2).

The effect of transferring patients with type 2 diabetes on prandial rapid-acting analogs (insulin aspart/lispro) in combination with bedtime NPH insulin to morning insulin glargine plus insulin aspart/lispro was also compared with the effect of continuation of the previous NPH treatment plus insulin aspart/lispro in a 6-month randomized trial. This trial demonstrated that bedtime insulin glargine improved glycemic control (HbA1c −0.6% vs −0.1%; P < .01) without an increase in hypoglycemia.

Table 2 – Treatment effects of insulin analogs in a basal-bolus regimen

<table>
<thead>
<tr>
<th></th>
<th>HbA1c change (%)</th>
<th>FPG within-subject variability (mg/dL)</th>
<th>Weight change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haak27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin detemir/insulin aspart</td>
<td>−0.2</td>
<td>23.4a</td>
<td>1.0a</td>
</tr>
<tr>
<td>NPH insulin/insulin aspart</td>
<td>−0.4</td>
<td>25.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Raslová28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin detemir/insulin aspart</td>
<td>−0.65</td>
<td>21.6b</td>
<td>0.51a</td>
</tr>
<tr>
<td>NPH insulin/insulin aspart</td>
<td>−0.58</td>
<td>27.7</td>
<td>1.13</td>
</tr>
</tbody>
</table>

HbA1c, hemoglobin A1c; FPG, fasting plasma glucose. Significant treatment difference: a P < .05, b P < .001.
cemia (0.78 to 0.79 episodes/patient-month) compared with NPH insulin treatment.\textsuperscript{29}

**OBSERVATIONAL TRIAL DATA**

Large observational studies can play an important role in investigating treatment outcomes in large, heterogeneous populations, because they provide real-life data that complement the results from randomized controlled trials. Many large observational studies have investigated the safety and effectiveness of insulin analogs.

**Type 1 diabetes.** Insulin analogs have been proven to have good tolerability and improve glycemic control without an increase in hypoglycemia in patients with type 1 diabetes in routine clinical practice.\textsuperscript{30,31} The PREDICTIVE study is a large, multinational observational study that investigated the safety and efficacy of insulin detemir in clinical practice.\textsuperscript{30,31}

The PREDICTIVE European cohort (N = 20,531) included 7420 patients with type 1 diabetes. Of these patients, a subgroup of 4782 switched either from a basal-bolus regimen with NPH insulin or insulin glargine to insulin detemir basal-bolus therapy, or from a human insulin basal-bolus regimen to insulin detemir-insulin aspart regimen.\textsuperscript{30} Significant improvements in glycemic control were seen for all patients (P < .0001), with HbA\textsubscript{1c} levels decreasing by 0.5%, 0.4%, and 0.6% in patients previously receiving NPH insulin, insulin glargine, and human basal-bolus insulins, respectively. Glycemic control was attained with a significant reduction in major hypoglycemia (55%, 51%, and 54%, respectively; P < .0001) and no weight gain.

**Type 2 diabetes.** Several observational studies have also investigated the safety and effectiveness of insulin analogs in routine clinical practice for the treatment of type 2 diabetes. The PREDICTIVE European cohort (N = 20,531) included 12,981 patients with type 2 diabetes,\textsuperscript{32} of which a subgroup of 293 patients transferred from a regimen of OAD therapy plus 1 or 2 basal injections of NPH insulin or insulin glargine to a regimen of OAD therapy plus insulin detemir, significantly improving glycemic control (Table 3). A lower incidence of hypoglycemia was also seen, with a significant decrease in body weight.\textsuperscript{32}

The long-term effectiveness and safety of insulin glargine was further investigated in a large observational study of 12,216 patients with type 2 diabetes inadequately controlled by OAD therapy,\textsuperscript{33} in which the addition of insulin glargine to OAD therapy resulted in improved glycemic control (HbA\textsubscript{1c} reduced by 1.7%; fasting plasma glucose [FPG], −70.2 mg/dL). This improvement was achieved without an increase in body weight and with a relatively small risk of hypoglycemia (0.1% of patients).\textsuperscript{33}

Premixed insulin analogs are also routinely prescribed for the treatment of type 2 diabetes. In PRESENT, a large, multinational observational study of 22,857 patients with type 2 diabetes previously uncontrolled on OADs or OAD therapy, BIAsp 70/30 was shown to be safe and effective for the treatment of type 2 diabetes.\textsuperscript{34} BIAsp 70/30 therapy resulted in significantly improved glycemic control for all patients. However, improvements were greater for insulin-naive patients than for those previously treated with insulin (HbA\textsubscript{1c} reduced by −2.2% and −1.6%, respectively; P < .05 for both). FPG and PPG levels were significantly reduced in both insulin-naive patients (−81 mg/dL and −122.4 mg/dL, respectively; P < .05 for both) and in those previously treated with insulin (−52.2 mg/dL and −90 mg/dL, respectively; P < .05 for both). Target HbA\textsubscript{1c} levels were attained by 28% of patients, but insulin-naive patients achieved these targets at a lower dose of BIAsp 70/30. Frequency of hypoglycemic events was also higher for patients previously treated with insulin than for insulin-naive patients (−2.35 vs −2.18 episodes/patient-year).\textsuperscript{34}

**INSULIN DELIVERY DEVICES**

Traditional insulin “vial and syringe” delivery has several disadvantages, including the potential for dosing inaccuracies—particularly among children or elderly patients who may have difficulty handling a vial and syringe or selecting the appropriate dose. Injection anxiety and social embarrassment may also have a negative impact on patient adherence.\textsuperscript{35,36}

These disadvantages are now being overcome by advances in insulin delivery devices.

The introduction of insulin pens in the 1980s greatly increased the flexibility and convenience of insulin administration.\textsuperscript{37} They are also associated with less painful injections and less social embarrassment, thereby increasing patients’ quality of life.\textsuperscript{38}

In a randomized crossover trial that assessed insulin-treated patient preference for a prefilled disposable pen device (FlexPen\textsuperscript{38} [Novo Nordisk A/S]) versus vial and syringe, 85% of patients thought the pen was more discreet for public use.\textsuperscript{39} Furthermore, usability and patient preference were compared for 4 prefilled, disposable, insulin pens (Solostar\textsuperscript{39} [sanofi aventis], Humulin\textsuperscript{39}/Humalog\textsuperscript{39} [Eli Lilly and Company], FlexPen, and a prototype pen [sanofi aventis]).\textsuperscript{40} Both the Solostar pen and FlexPen were found to have high patient usability, with 94% and 90% of patients, respectively, successfully completing the usability assessment test (patients prepared each pen for injection into a receptacle). A higher proportion (P < .05) of patients expressed an overall preference for the Solostar pen (53%) compared with FlexPen (31%) and Humulin/Humalog (15%), as determined during a...
question-and-answer session. Patients found the Solostar pen easier to use properly, and they appeared to prefer the tactile feel of the Solostar pen compared with the FlexPen and Humulin/Humalog pen.40

However, recently the injection force of the Next Generation FlexPen® (NGFP), a modified version of FlexPen, was compared with that of Solostar.41 This study compared the injection force of 24 pens of each type during the delivery of 60 IU of insulin at 3 constant push-button speeds. It was observed that NGFP had an 18% to 45% lower injection force compared with Solostar.41

Prefilled insulin pens, in particular, are associated with improved treatment adherence versus the vial and syringe,35 resulting in improved glycemic control, lower incidence of hypoglycemic events, and better long-term clinical outcomes.35 A study of 1156 patients with type 2 diabetes previously treated with human insulin or an insulin analog administered with a vial and syringe evaluated the effect on adherence of transferring to a prefilled analog pen device.35 Switching from the vial and syringe to a pen was shown to significantly improve treatment adherence (as measured by a medication possession ratio ≥ 80%) from 62% to 69% (P < .01). The likelihood of experiencing hypoglycemic events also fell by 50% when a prefilled insulin pen was used (P < .05).

Pen devices also utilize small-gauge needles, making them much more comfortable to use than traditional syringes.42 In a comparison of 2 types of needle design and diameter (NovoFine® 32G 6-mm [Novo Nordisk A/S] and Micro Fine Plus® 31G 5-mm [Nippon Becton Dickinson Co Ltd]) in patients with diabetes, both factors played an important role in reducing injection pain.43 On a questionnaire used by Iwanaga and Kamoi43 with a scale ranging from −100 to +100, in which a higher score indicated a better outcome, use of a tapered needle (NovoFine) was associated with less painful insertions, less bruising, and less bleeding than the standard needle (Micro Fine Plus). The tapered needle was also rated as more convenient and easy to use.43

CONCLUSIONS
Insulin analogs have greatly improved type 1 and type 2 diabetes

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Table 3 – Observed changes after 14 weeks of insulin detemir therapy: results of the PREDICTIVE study31

<table>
<thead>
<tr>
<th></th>
<th>NPH group</th>
<th>Glargine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>Baseline</td>
<td>8.1 ± 1.4</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>−0.2 ± 1.2a</td>
<td>−0.6 ± 0.9b</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>Baseline</td>
<td>153 ± 39.6</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>−18.0 ± 39.6b</td>
<td>−25.2 ± 43.2b</td>
</tr>
<tr>
<td>Fasting glucose variability (mg/dL)</td>
<td>Baseline</td>
<td>23.4 ± 21.6</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>−7.2 ± 19.8b</td>
<td>−5.4 ± 18.0b</td>
</tr>
<tr>
<td>Overall hypoglycemia (episodes/patient-year)</td>
<td>Baseline</td>
<td>11.7</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>−8.7b</td>
<td>−3.5c</td>
</tr>
<tr>
<td>Nocturnal hypoglycemia (episodes/patient-year)</td>
<td>Mean change from baseline</td>
<td>−5.5b</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>Mean change from baseline</td>
<td>−0.7c</td>
</tr>
</tbody>
</table>

NPH, neutral protamine hagedorn; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose.

Data are mean (SD) vs baseline: a P < .05, b P < .0001, c P < .01.
by mimicking the physio-
logical insulin profile more closely than traditional insulins. While rapid-acting insulin analogs were developed to replace prandial insulin and to mimic the physiological response to ingestion of food, long-acting analogs supplement or replace basal insulin to mimic the constant physiological re-
lease of insulin seen in healthy persons between meals. Premixed insulin analogs were later developed to sup-
plement both prandial and basal in-
nulin needs in a more convenient and effective way. Numerous clinical trials and observational studies have dem-
onstrated the advantages of insulin analogs over human insulin regi-
mens, and insulin analogs are associ-
ated with an improved balance be-
tween glycemic control and tolerabil-
ity compared with human insulin. The advances in insulin preparations have also encouraged the improve-
ment of insulin delivery devices such as pens, which leads to improved treatment satisfaction and medication adherence, resulting in better clinical outcomes.

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