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## Using Insulin Effectively in the Management of Diabetes

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Since its discovery and first therapeutic use on January 11, 1922 at the Toronto General Hospital, insulin has been a life-saving therapy for type 1 diabetes and an important option for managing type 2 diabetes.<sup>1</sup> Over the past 80 years, improved understanding of the physiology of insulin has led to the development of designer insulin analogues and novel delivery systems. Despite these advances, however, the ultimate therapeutic goal of sustained euglycemia and avoidance of hypoglycemia in patients with diabetes remains largely unrealized.<sup>2</sup> This issue *Endocrinology Rounds* reviews current concepts and knowledge regarding the effective use of insulin in the management of diabetes.

### The principles of insulin replacement

Insulin replacement strategies in diabetes ideally aim to achieve sustained euglycemia through a faithful imitation of the normal pancreatic secretion of insulin. Thus, to appreciate the rationale underlying current insulin replacement strategies, an understanding of the biology of endogenous insulin secretion is very useful.

In normal physiology, insulin is secreted by pancreatic  $\beta$ -cells into the portal venous system. Despite wide fluctuations in nutrient intake and energy expenditure, healthy individuals maintain plasma glucose concentrations within a narrow range of 3.5 – 7.0 mmol/L throughout the day (Figure 1)<sup>3</sup>. This blood glucose homeostasis is the result of tightly-regulated insulin secretion consisting of 2 components:

- a basal secretion rate
- surges of markedly increased secretion following carbohydrate ingestion.

The basal secretion of ~1 u/hr constitutes ~40% of total 24-hour pancreatic insulin output and serves to limit hepatic glucose production and adipocyte lipolysis in the post-absorptive state (eg, between meals and overnight).<sup>4</sup> Following carbohydrate ingestion, dietary secretagogues and gastrointestinal hormones, such as glucagon-like-peptide 1, stimulate abrupt pulses of insulin secretion that are up to 5 times the basal rate. These pulses serve to regulate postprandial glycemia by inhibiting hepatic glucose production and increasing peripheral glucose uptake.

To use insulin effectively in the management of diabetes, the task at hand is to replicate this complex physiology. As such, in patients with type 1 diabetes, in whom endogenous insulin secretion is absent, insulin replacement strategies aim to faithfully imitate both basal secretion and the appropriately timed prandial surges seen in non-diabetic individuals. Typically, one component of the treatment regimen serves as *basal insulin*, while a second component provides *meal insulin*. Depending on the degree of  $\beta$ -cell secretory insufficiency, similar considerations may apply to insulin replacement in patients with type 2 diabetes as well. In either disease context, important factors to consider in the design of the treatment regimen include the types of insulin to be used for basal and meal coverage and the method of delivery.

### Insulin preparations: human insulin and analogues

**Meal insulins:** Regular human insulin, the first medication to be commercially manufactured using recombinant DNA technology, is identical to the endogenous insulin polypeptide.<sup>5</sup> An important property of regular insulin, however, is its tendency to self-associate in solution, leading to the formation of dimers and subsequently hexamers. Since the absorption of hexameric insulin molecules is delayed following subcutaneous injection (pending dissociation into monomers and dimers<sup>6</sup>), the pharmacokinetic profile of regular insulin is characterized by:



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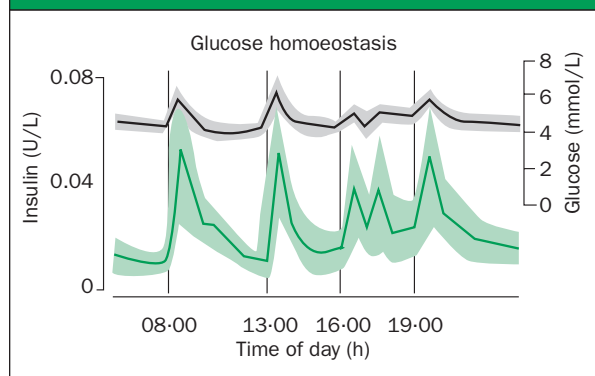
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**Figure 1: Profiles of plasma glucose and insulin over 24 hours in healthy individuals (n=12)<sup>3</sup>**



- a modestly delayed onset of biologic action in vivo (30-60 minutes after injection)
- a relatively late peak effect (2-4 hours after injection)
- a prolonged duration of action (6-8 hours) (Table 1).<sup>7</sup>

The delayed absorption of regular insulin compromises its effectiveness in mimicking the normal prandial insulin surge. As such, it follows that an analogue with enhanced absorption may provide a superior meal insulin. With this idea in mind, it was previously noted with interest that human insulin-like growth factor-1 (IGF-1) – despite significant homology to insulin – displayed a reduced tendency to form multimers. On further study, it was revealed that differences between 2 specific amino acid residues mediated the relative multimerization potential of IGF-1 and insulin.

**Lispro:** Manipulation of these residues led to the development of lispro insulin, the first commercially available analogue.<sup>8</sup> The structure of lispro is identical to that of human insulin except for a reversal of the 28<sup>th</sup> and 29<sup>th</sup> amino acid residues (proline and lispro, respectively) of the normal insulin B-chain. Because the resultant conformational change introduces steric hindrance at interfaces involved in dimerization, dimer formation with lispro is reduced by a factor of 300 compared to regular human insulin.<sup>9</sup> As such, clinically, lispro acts similarly to monomeric human insulin. Lispro is rapidly absorbed within 10-15 minutes, reaches peak activity in 60-90 minutes, and has a total duration of action of 3-5 hours (Table 1).<sup>10</sup> Not surprisingly, this pharmacokinetic profile allows lispro to better mimic the normal prandial insulin surge than regular human insulin.

**Insulin aspart:** A second rapid-acting analogue, insulin aspart, uses a different approach to reduce self-association of insulin molecules. Insulin aspart was designed by replacing the proline residue at position 28 of the B-chain of insulin with aspartic acid. The negatively-charged aspartic acid residue causes repulsion from other negatively-charged amino acids and thereby reduces self-association amongst insulin aspart monomers.<sup>11</sup> As such, insulin aspart displays a similar pharmacokinetic profile to that of lispro and is also well-suited for use as meal insulin (Table 1).<sup>12</sup>

**Insulin glulisine:** A third rapid-acting analogue is insulin glulisine (Lys<sup>B33</sup>, Glu<sup>B29</sup>).<sup>13</sup> This preparation is not yet available in Canada, but is expected to provide another meal insulin option.

**Table 1: Approximate pharmacokinetic properties of human insulin and insulin analogues after subcutaneous injection**

Insulin preparation	Onset of action	Peak of action	Duration of action
<b>Meal insulin</b>			
Lispro	10-15 mins	1 – 1.5 hrs	3 – 5 hrs
Aspart	10-15 mins	1 – 2 hrs	3 – 5 hrs
Regular	30-60 mins	2 – 4 hrs	6 – 8 hrs
Glulisine	10-15 mins	1 – 1.5 hrs	3 – 5 hrs
<b>Basal insulin</b>			
NPH	2.5 – 3 hrs	5 – 7 hrs	13 – 16 hrs
Lente	2.5 – 3 hrs	7 – 12 hrs	up to 18 hrs
Ultralente	3 – 4 hrs	8 – 10 hrs	up to 20 hrs
Detemir	2 – 3 hrs	6 – 8 hrs	~ 24 hrs
Glargine	2 – 3 hrs	no peak	~ 24 hrs

The pharmacokinetics of the rapid-acting insulin analogues (lispro and aspart) suggest that they should provide superior meal coverage compared to regular human insulin. The rapid onset of action of lispro and aspart allows patients to inject these analogues immediately before meals, rather than 30 minutes preprandially, as recommended with regular insulin. This feature is associated with greater meal-time flexibility, easier application of carbohydrate estimation techniques, and improved quality of life.<sup>14</sup> Furthermore, both lispro and aspart provide better postprandial glycemic control with less postprandial and nocturnal hypoglycemia compared to regular insulin.<sup>15-17</sup> Use of these rapid-acting analogues in intensive insulin regimens, however, has not been consistently associated with substantial improvement in A1c compared to regular insulin.<sup>14</sup> This inconsistency is likely due to the sub-optimal postabsorptive coverage provided by the basal insulins used in the studies in question. Specifically, given their shorter duration of action, the rapid-acting analogues may expose inadequate basal coverage between meals that would otherwise be masked by the longer duration of action of regular insulin. In any event, even in the absence of an A1c benefit, the consistent observation of improved postprandial glycemia with less hypoglycemia suggests an overall reduction in glycemic excursion and therefore better glycemic control around meals with rapid-acting analogues.

### Basal insulins

The goal of basal insulin preparations is to mimic the effects of the basal component of normal pancreatic insulin secretion. As such, the ideal basal insulin would have a peakless, 24-hour time-action profile. Initial attempts to achieve this goal sought to reduce the rate of absorption of exogenous insulin from subcutaneous tissue by manipulating its suspension.

**NPH insulin:** Neutral protamine hagedorn (NPH) insulin is a suspension of insulin complexed with protamine and zinc.<sup>18</sup> As NPH insulin is poorly absorbed from subcutaneous tissue, its pharmacokinetic profile is characterized by a:

- delayed onset of action (2.5-3 hours)
- late peak effect (5-7 hours)
- prolonged duration of action (13-16 hours) (Table 1).<sup>7</sup>

**Lente insulin:** Similarly, lente insulin, a crystalline suspension of insulin with zinc and acetate, is another intermediate-acting preparation that exhibits a comparable pharmacokinetic profile to that of NPH, though with a slightly later peak and longer duration of action.

**Ultralente,** also a zinc insulin suspension, represents a long-acting preparation, with onset of action 3-4 hours after injection, peak effect at 8-10 hours, and duration of action of up to 20 hours (Table 1).<sup>7</sup>

One problem with the intermediate- and long-acting human insulin preparations is their substantial variation in subcutaneous absorption both within an individual patient and between patients, resulting in variable glycemic excursions.<sup>19</sup> Indeed, with NPH and lente, variability in absorption may account for as much as 80% of day-to-day variation in blood glucose concentrations.<sup>20</sup> Secondly, the peak effect of these preparations is an undesirable quality in basal insulin.

Recognizing the limitations of these basal insulin preparations, developers of long-acting insulin analogues have manipulated the structure of insulin with the goal of achieving slow, prolonged absorption following subcutaneous injection.

**Insulin glargine:** The first commercially-available, long-acting analogue – insulin glargine – was introduced to the U.S. market in 2001. (Although it is approved, it is still not available in Canada). Glargine has 2 modifications compared with human insulin: 2 arginines have been added to the carboxy terminus of the B chain and a glycine residue replaces an acid-sensitive asparagine at position A21.<sup>21</sup> By shifting its isoelectric point towards neutrality, these changes render glargine completely soluble in its acidic injection solution at pH 4.0, but much less soluble at the neutral physiologic pH of subcutaneous tissue. Following injection into the subcutaneous tissue, the acidic injection solution is neutralized, causing glargine to form micro-precipitates.<sup>22</sup> The subcutaneous microprecipitates cause glargine to be absorbed slowly into the systemic circulation, thereby providing a smooth and gradual rise in its serum concentration. As such, glargine exhibits an onset of action 2-3 hours after injection with a relatively peakless, 24-hour duration of action (Table 1).<sup>23</sup> Importantly, glargine is associated with less variability in absorption than either NPH or lente,<sup>24,25</sup> while retaining an *in vivo* hypoglycemic potency that is equivalent to human insulin. In clinical trials in patients with type 1 diabetes, the use of glargine as basal insulin in intensive therapy was associated with lower fasting plasma glucose levels and less hypoglycemia (including nocturnal hypoglycemia) compared with NPH.<sup>26-28</sup> A single study also demonstrated improved A1c with glargine compared to NPH.<sup>29</sup>

**Insulin detemir:** A second long-acting analogue is insulin detemir, engineered through removal of the B30 amino acid and acylation of a 14-carbon aliphatic fatty acid to the B29 residue.<sup>30</sup> The significance of this modification is that it allows for reversible binding between albumin and the fatty acid. As such, after injection, an equilibrium develops between free and bound detemir, in that most of the analogue is bound to albumin. Since only the free analogue binds to the insulin receptor, the sustained release of

bound detemir from circulating albumin leads to a prolonged duration of action.<sup>31</sup> Insulin detemir exhibits peak activity 6-8 hours after injection and a prolonged 24-hour duration of action.<sup>31</sup> Although detemir is not yet commercially available, its use as basal insulin in intensive regimens in limited studies to date has been associated with significant reductions in hypoglycemia compared to NPH.<sup>19</sup> In addition, studies suggest that glycemic control is more predictable with detemir than with NPH, with significantly less within-subject variation in blood glucose levels.<sup>32,33</sup>

## Intensive insulin therapy

The Diabetes Control and Complications Trial (DCCT) demonstrated that the use of intensive insulin therapy is associated with lower A1c concentrations and a reduction in the risk of microvascular complications in patients with type 1 diabetes.<sup>34</sup> Intensive therapy, currently recommended in all patients with type 1 diabetes, can be provided in 1 of 2 ways: multiple daily injections (MDI) of insulin or continuous subcutaneous insulin infusion (CSII). With both regimens, the goal is to imitate physiologic insulin secretion through appropriate meal and basal insulin replacement.

### Multiple daily injection (MDI) therapy

An MDI regimen requires at least 4 subcutaneous injections of insulin per day, consisting of boluses of meal insulin preprandially and at least 1 injection of basal insulin, usually at bedtime. As indicated in the 2003 Canadian Diabetes Association (CDA) Clinical Practice Guidelines, the preferred meal insulin is a rapid-acting analogue.<sup>35</sup> In MDI therapy, the use of rapid-acting analogues has been associated with better postprandial glycemic control, a decreased incidence of hypoglycemia, and improvements in quality of life, compared to regular insulin.<sup>14</sup> Although, as noted earlier, improvements in A1c have not been consistently observed when comparing analogues with regular insulin in MDI therapy, this phenomenon likely reflects sub-optimal basal insulin replacement in the studies in question.

Basal insulin replacement in MDI has typically been provided in the past by NPH, lente, or ultralente. In clinical studies of MDI regimens using rapid-acting analogues as meal insulin, these basal preparations have been associated with similar glycemic control and hypoglycemic risk.<sup>36,37</sup> In the near future, however, long-acting analogues are likely to become the basal insulins of choice in MDI therapy. In studies comparing glargine and NPH as basal insulins in MDI regimens in type 1 diabetes, glargine has been associated with lower fasting glucose levels and less hypoglycemia.<sup>26-28</sup> Indeed, in the 2003 CDA Clinical Practice Guidelines, it is recommended that glargine be considered for use as basal insulin in well-controlled patients with elevated fasting glucose levels or problems with overnight hypoglycemia.<sup>35</sup> In addition, glycemic control has been shown to be similar with a single injection of glargine at breakfast, dinner, or bedtime, in studies using lispro as meal insulin in MDI regimens.<sup>38</sup> Importantly, few studies to date have compared long-acting analogues and NPH in MDI regimens using only rapid-acting analogues for meal

insulin, although 1 such study demonstrated reduced A1c levels with a single dose of glargine compared to 4 daily injections of NPH.<sup>39</sup> Furthermore, Hermansen and colleagues recently reported improved A1c and less hypoglycemia with detemir and aspart for basal-bolus therapy, compared to NPH and regular insulin, in an 18-week, open-label trial in 595 patients with type 1 diabetes.<sup>40</sup> Overall, it is expected that the combination of rapid-acting analogues for meal insulin and long-acting analogues for basal coverage will provide the most physiologic insulin replacement to date amongst MDI regimens in patients with type 1 diabetes.

### Continuous subcutaneous insulin infusion (CSII)

In CSII therapy, an external infusion pump is used to deliver a continuous infusion of rapid- or short-acting insulin into the subcutaneous tissue of the abdominal wall. Basal insulin replacement is provided by continuous delivery of insulin by the pump at a pre-programmed rate. Meal insulin is provided by bolus delivery of insulin using the pump, as triggered by the patient prior to a meal. As indicated in the 2003 CDA Clinical Practice Guidelines,<sup>35</sup> the insulin of choice in CSII is a rapid-acting analogue since both lispro and aspart have been shown to reduce postprandial glycemia, A1c concentration, and the incidence of hypoglycemia compared with regular insulin in this setting.<sup>41-43</sup>

CSII offers advantages over MDI therapy in regards to convenience and flexibility. Unlike MDI, the rate of basal infusion with CSII can be immediately adjusted at any given time. Moreover, the capability for multiphasic basal settings on current insulin pumps makes it possible for the user to set varying rates of basal insulin replacement at different times of the day depending on requirements. On the other hand, an important limitation with CSII is the significant cost associated with both the pump and necessary supplies. Another issue is infection at the insertion site of the catheter, estimated to occur at a rate of 7.3 to 11.3 events per 100 years of patient follow-up.<sup>44,45</sup> Generally, these infections are readily treatable with antibiotics and a change of insertion site. Finally, if basal insulin delivery is interrupted due to either pump malfunction or catheter disruption, hyperglycemia or even ketoacidosis may occur in patients with type 1 diabetes, who may quickly become markedly insulinopenic owing to the use of only rapid- or short-acting insulin in CSII.<sup>46</sup> Ultimately, the choice between MDI and CSII is generally determined by patient-driven factors (eg, lifestyle issues, finances, and personal preference).

### Clinical efficacy of CSII versus MDI

In clinical trials comparing optimized MDI regimens with CSII, glycemic control has been found to be similar with both regimens. In the DCCT, mean A1c was 0.2% lower in the cohort of intensively-treated patients who had primarily used CSII when

compared to their counterparts on MDI therapy.<sup>45</sup> While the incidence of severe hypoglycemia was similar between the 2 groups, the frequency of episodes resulting in coma or seizure was higher in the CSII cohort than in the MDI group. However, the DCCT results may offer a biased comparison of these 2 therapies since patients randomized to intensive therapy could choose between CSII and MDI and could switch between these regimens during the trial. Moreover, given the subsequent development of insulin analogues (not used in the DCCT), the applicability of these findings to current clinical practice is unclear. A similar issue is noted with a recent meta-analysis of trials comparing CSII and MDI regimens that reported a difference in A1c of 0.51% favouring CSII.<sup>47</sup> Indeed, all but 1 of the 12 studies included in the meta-analysis were older studies using sub-optimal, non-analogue meal insulins.

To date, in the few studies comparing CSII and optimized MDI therapy using rapid-acting analogues in type 1 diabetes, insulin pump therapy has been associated with slightly better glycemic control, with no significant difference in hypoglycemia.<sup>48-50</sup> The glycemic advantage of CSII over MDI in these studies may be related to baseline A1c, such that patients with the poorest initial glycemic control may experience the greatest benefit with insulin pump therapy. In all of these studies, NPH was the basal insulin for MDI therapy. As such, a comparison of CSII and optimized MDI regimens utilizing long-acting analogues for basal insulin and rapid-acting analogues for prandial coverage would be of clear interest. A recent chart audit of 103 patients reported similar glycemic control with both regimens using rapid- and long-acting insulin analogues.<sup>51</sup> A comparison of these therapeutic regimens by randomized controlled trial is needed.

### Routes of insulin delivery

With both MDI and CSII therapy, insulin is delivered into the patient's subcutaneous fat tissue. To date, however, the faithful imitation of normal physiologic insulin secretion generally has not been achieved with subcutaneous delivery of available insulin preparations. Limiting factors include:

- the pharmacokinetics of current insulin preparations following subcutaneous injection
- the systemic dissemination of the injected insulin via the peripheral venous system (in contrast to normal pancreatic secretion into the portal venous system)
- patient dissatisfaction with the demands of complex treatment regimens.

Thus, alternative routes for delivery of insulin have been explored.<sup>52</sup> Possibilities that have been considered include nasal, pulmonary, oral, buccal, transdermal, and peritoneal delivery. While these attempts have met with limited success to date, intrapulmonary and intraperitoneal delivery of insulin, in particular, may hold promise for the future.

## Insulin therapy in type 2 diabetes

The progressive nature of  $\beta$ -cell insufficiency in type 2 diabetes suggests that many patients will ultimately require insulin therapy. Insulin therapy is indicated when diet, exercise, and oral hypoglycemic agents are unable to achieve adequate glycemic control. Typically, bedtime basal insulin is introduced in conjunction with the daytime use of oral agents. The results of previous clinical trials suggest that the combination of metformin and bedtime NPH is superior to other regimens in regards to glycemic control, hypoglycemia, and prevention of weight gain.<sup>53,54</sup> It has also been shown that the combination of insulin with an insulin-sensitizing thiazolidinedione (TZD) can result in significant improvement in glycemic control and a reduction in insulin dose.<sup>55</sup> However, this combination can also result in slightly more fluid retention than that observed when using a TZD as monotherapy or in combination with metformin. At this time, the use of a TZD with insulin is not a labeled indication in Canada.

The issue of the ideal basal insulin preparation in type 2 diabetes was recently addressed in the Treat-to-Target trial that compared the randomized addition of bedtime glargine or NPH to oral therapy, with titration of the insulin dose to achieve a target fasting plasma glucose  $\leq 5.6$  mmol/L.<sup>56</sup> In this study, both basal insulin preparations were associated with similar fasting glucose levels and A1c, though glargine was associated with significantly less nocturnal and symptomatic hypoglycemia. Importantly, a majority of patients (~60%) were able to achieve A1c  $\leq 7\%$ . Thus, this study provided proof-of-concept that, when using the study algorithm for dose titration, bedtime basal insulin in combination with oral therapy can achieve the recommended A1c target in patients with type 2 diabetes and suggested that glargine may be superior to NPH as the basal insulin preparation in this setting. The 2003 CDA Clinical Practice Guidelines also support the use of glargine instead of NPH in this setting to reduce overnight hypoglycemia and weight gain.<sup>57</sup> If this approach does not yield adequate glycemic control, then intensification of insulin therapy with rapid-acting analogues for meal coverage should be considered.

## Conclusions

Although the goal of physiologic insulin replacement remains generally unrealized at this time, advances in insulin therapy have improved our ability to limit hyperglycemia and reduce complications in patients with diabetes. Insulin analogues with superior pharmacokinetics are now better able to provide near-physiologic basal and meal insulin supplementation than ever before. With further technological advances and clinical experience, physiologic insulin replacement may one day become a reality for patients with diabetes.

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## Upcoming Meetings

5-9 September 2004

### 40th Annual Meeting of the European Association for the Study of Diabetes

Munich, Germany

CONTACT: EASD

Tel.: 49 211 758 469 0

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or annual-meeting@easd.org

Website: www.easd.org

23-27 October 2004

### Canadian Cardiovascular Congress

Calgary, AB

CONTACT: Anne Ferguson, Executive Director

Tel.: 613-569-3407 ext. 403

Fax: 613-569-6570

Email: ferguson@ccs.ca

Website: www.cardiocongress.org

27-30 October 2004

### 8th Annual CDA/CSEM Professional Conference and Annual Meetings

The Canadian Diabetes Association (CDA)/Canadian Society of Endocrinology and Metabolism (CSEM)

Quebec City, Quebec

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