

# New treatments and treatment philosophy for type 1 diabetes

Advances in insulin types and regimens can help patients fit insulin therapy to their lifestyles.

**ABSTRACT:** Treatment of type 1 diabetes has changed over the past several decades. Recent advances include the development of insulin analogs, such as the long-acting insulin glargine and the ultra-short-acting insulins aspart and lispro, and various new treatment regimens and devices, such as multiple daily injection and insulin pump therapy. These advances have increased the flexibility of insulin therapy and improved glycemic control, thus preventing and reducing diabetes-related complications.

**A**dvances in the treatment of type 1 diabetes (T1D) in the past decade have occurred in the areas of treatments and treatment philosophy. The push for new insulin analogs such as glargine, aspart, and lispro came in part from the results of the Diabetes Control and Complications Trial (DCCT), which highlighted the importance of more physiological insulin profiles.

## Prevention of complications in type 1 diabetes

The importance of glycemic control in preventing microvascular complications of T1D was clearly demonstrated by the results of the DCCT in 1993.<sup>1</sup> The DCCT was a 9-year study examining the effect of conventional insulin therapy compared with the effect of intensive insulin therapy on complications related to diabetes. Intensive insulin therapy consisted of either multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII) therapy. The DCCT saw a lower mean glycosylated hemoglobin value achieved in the intensive group compared with the conventional therapy group (7.2% vs 9.1%,  $P < .001$ ).

The two target populations in the study included a primary prevention

group consisting of patients with no retinopathy or nephropathy, and a secondary prevention group of patients with established microvascular complications. Intensive therapy reduced the adjusted mean risk of retinopathy by 76% (95% CI, 62% – 85%) in the primary prevention group. In the secondary prevention arm of the study, the incidence of retinopathy was higher in the intensive group at 1 year, but the intensively treated group had lower average risk of progression during the entire study period by 54% (95% CI, 39% – 66%). Intensive therapy reduced the mean adjusted risk of microalbuminuria by 34% (95% CI, 2% – 56%) in the primary prevention cohort and by 43% (95% CI, 21% – 58%) in the secondary prevention cohort. There was a nonsignificant trend toward fewer cardiovascular events in the intensively treated group (3.2 vs 5.4%,  $P = .08$ ).

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At the end of the DCCT study, most patients were followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study,<sup>2</sup> a long-term observational study comparing the effect of intensive therapy and conventional therapy during the DCCT on the long-term outcomes of retinal and renal complications. **Table 1** summarizes the risk reduction and odds reduction achieved with intensive insulin therapy in the DCCT and the follow-up EDIC studies.<sup>3,4</sup>

Intensive insulin therapy for managing T1D may also be considered good value in terms of cost-effectiveness by reducing complications and improving quality of life.<sup>5,6</sup> However, one significant side effect of intensive insulin therapy is hypoglycemia. In the DCCT, the incidence of hypoglycemia, including severe hypoglycemic events, in the intensively treated subjects ranged from two to six times that observed in the conventionally treated subjects.<sup>7</sup> Another undesirable effect of intensive insulin therapy seen in the DCCT was weight gain. Subjects receiving intensive treatment gained more weight (5.1 +/- 4.6 kg) than subjects receiving standard therapy (2.4 +/- 3.7 kg, *P*<.0001) during the first year of therapy.<sup>8</sup> The dilemma posed by the results of the DCCT is that better glycemic control and reduced complications seemed to come at the expense of weight gain and increased frequency of hypoglycemia. The development of new insulin analogs has made the challenge of reproducing physiological insulin secretion in order to achieve optimal glycemic control with minimal hypoglycemia more attainable.

### New insulin analogs

In general, all individuals require basal insulin to decrease hepatic gluconeogenesis and prevent development of ketosis. Boluses of short- or

**Table 1. Risk reduction and odds reduction (95% CI) with intensive therapy.**

Complication	Risk reduction (95% CI) after 6.5 years in DCCT %	Odds reduction (95% CI) after 4 additional years in EDIC %
<b>Retinopathy</b>		
Three-step worsening*	63 (52 – 71)	76 (52 – 88)
Proliferative or severe nonproliferative	47 (15 – 67)	74 (46 – 87)
Macular edema	26 (-8 – 50)	77 (52 – 89)
Laser therapy	51 (21 – 70)	77 (45 – 91)
<b>Nephropathy</b>		
Microalbuminuria (>40 mg/24 h)	39 (21 – 52)	53 (26 – 70)
Proteinuria (>300 mg/24 h)	54 (19 – 74)	86 (60 – 95)

\*Three-step worsening is defined as a three-category change on the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale.<sup>3,4</sup>

**Table 2. Long-acting or intermediate-acting insulin.<sup>10</sup>**

Type	Onset (hours)	Peak (hours)	Effective duration (hours)	Approximate price (varies by pharmacy)
NPH	2 – 4	4 – 10	10 – 16	\$20 (10 cc vial) \$40 (5x3 cc penfill)
Lente	2 – 4	4 – 12	12 – 18	\$20 (10 cc vial)
Ultralente	6 – 10	10 – 16	18 – 24	\$20 (10 cc vial)
Glargine*	2 – 4	No peak	20 – 24	US\$60 (10 cc vial)

\*Not yet available in Canada.

rapid-acting insulin are added to treat postprandial hyperglycemia. The peak and duration of effect for each type of insulin are determined by its absorption profile. Under physiological conditions, insulin molecules tend to self-associate into dimers and hexamers once injected subcutaneously. A major factor determining absorption rate into the systemic circulation of insulin preparations is the dissociation time of hexamers to dimeric and monomeric insulin units. There is also variability in insulin action depending on the

site of injection.<sup>9</sup> The various types of insulins and their respective profiles are summarized in **Table 2** and **Table 3**.

### Long-acting insulin (glargine)

The newest long-acting insulin, glargine (Lantus; currently available in the United States), is an insulin analog that is slowly absorbed and is virtually peakless. It differs from human insulin in that it replaces the amino acid asparagine by glycine at position A21, and adds two arginine residues to the C-terminus of the B-chain.

Glargine is soluble prior to injection but after subcutaneous injection the change to physiological pH leads to its precipitation. This stabilizes its hexameric form and delays dissociation into dimers and monomers. Because of its very long duration of action, insulin glargine is taken only once daily, usually at bedtime as a basal insulin. It has been shown to decrease the incidence of nocturnal hypoglycemia.<sup>11</sup> It cannot be mixed in a syringe with any other type of insulin. Its long-term safety and its suitability for use in pregnancy and lactation have not yet been established.

### Short-acting insulins (aspart and lispro)

The two new ultra-short-acting insulins, aspart (Novorapid) and lispro (Humalog), are insulin analogs that are rapidly absorbed and have the fastest peak of all insulin types. These analogs are designed to mimic the first phase of insulin secretion and thus are optimal for meal-related bolus administration. They should be administered immediately before meals to match the rate of postprandial hyperglycemia. This is in contrast to regular insulin, which is taken subcutaneously at least 30 minutes before a meal to achieve the same effect. Both of these insulin analogs have been formulated by amino acid substitutions in the insulin molecule.

Insulin aspart is the result of a replacement of proline by aspartic acid at position B28, which consequently reduces formation of dimers and hexamers. It is more rapidly absorbed after subcutaneous injection than regular insulin, with a peak concentration occurring approximately 1 hour after injection.

Insulin lispro is the result of a reversal of amino acids at positions 28 and 29 on the insulin B-chain. This change also reduces the tendency of

Table 3. Short-acting or rapid-acting insulin.<sup>10</sup>

Type	Onset (minutes)	Peak (hours)	Effective duration (hours)	Approximate price (varies by pharmacy)
Lispro	5 – 15	0.5 – 1.5	2 – 5	\$30 (10 cc vial) \$60 (5x3 cc penfill)
Aspart	5 – 15	0.5 – 1.5	2 – 5	\$30 (10 cc vial) \$60 (5x3 cc penfill)
Regular	30 – 60	2 – 4	5 – 8	\$20 (10 cc vial) \$40 (5x3 cc penfill)

the insulin molecule to form dimers and hexamers, thus increasing the absorption rate of insulin monomers after injection. Lispro lowers blood sugar the most approximately 1 hour after it is injected.

### Treatment philosophy in type 1 diabetes

The goals of insulin therapy in T1D are to optimize glycemic control while minimizing hypoglycemia. The most recent Canadian Diabetes Association clinical practice guidelines ([www.diabetes.ca/cpg2003](http://www.diabetes.ca/cpg2003)) continue to emphasize tight glycemic control for patients with T1D. Various insulin regimens have been used to achieve this goal, with some being more physiological, more flexible, and consequently more successful than others.

#### Twice-daily dosing

This regimen consists of a mix of short- and long-acting insulin in the morning and again in the evening. The mixing of short- and long-acting insulin is usually done immediately before injection. Examples of premixed combinations of regular/NPH insulin include 30/70, 20/80, and 10/90. These premixed insulins are a reasonable compromise for elderly or handicapped patients who are not able to mix insulins. In general, premixed

insulins are not recommended for managing T1D as their fixed ratios have limited usefulness. Patients using twice-daily regimens with premixed insulin rarely achieve optimal glycemic control because these strategies do not provide physiological or flexible insulin replacement. Moreover, lack of flexibility in timing of injections and meals may increase risk of hypoglycemia.

#### Multiple daily injection

Multiple daily injection (MDI) is a strategy that is widely used to achieve optimal glycemic control in T1D. Improved glycemic control is possible with MDI in conjunction with frequent self-monitoring of blood glucose. The advantages of MDI therapy include improved physiological and flexible insulin administration, particularly when used in combination with carbohydrate counting to determine meal-time insulin doses and correction boluses of insulin for episodes of hyperglycemia. There is also evidence demonstrating that MDI therapy using short-acting insulin for meals and intermediate-acting (NPH) insulin at bedtime is associated with less hypoglycemia and better glycemic control than using NPH at supper-time.<sup>12</sup>

There are a number of different ways to start MDI therapy. Suggested

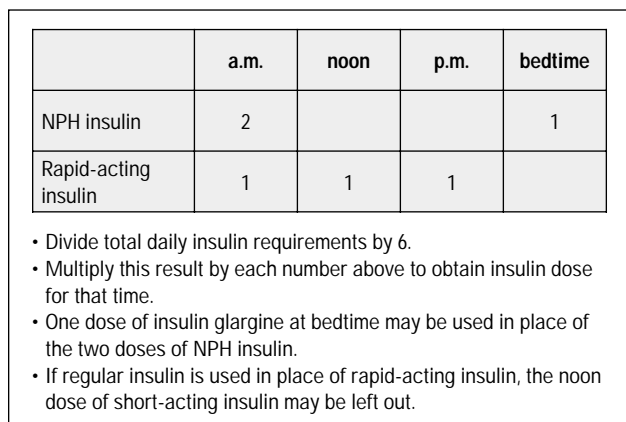


Figure 1. How to start MDI: "Rule of 6."

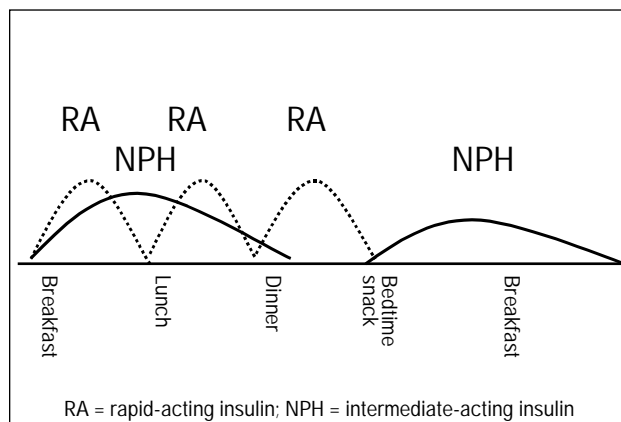


Figure 2. Insulin action profile for "Rule of 6."

"rules" and insulin action profiles can be seen in Figures 1-4. These examples of starting regimens can be adjusted according to the results of subsequent blood glucose monitoring.

**Continuous subcutaneous insulin infusion**

Continuous subcutaneous insulin infusion (CSII) using a small programmable pump device is an alternative to the MDI strategy (Figure 5). This form of insulin replacement closely approximates the physiological pattern of secretion. It is a therapeutic option for management of problems such as the dawn phenomenon that results in morning hyper-

glycemia or nocturnal hypoglycemia. It is also useful for patients who desire improved glycemic control and flexibility in work, lifestyle, and eating, especially if schedules are erratic or unpredictable, as in the case of shift workers or those with active lifestyles. Basal insulin in short-acting form is delivered by the infusion pump continuously and at specific rates; bolus insulin is delivered after the patient determines the amount of insulin to be taken with a meal (Figure 6). The amount of insulin taken with each meal depends on the blood glucose monitoring result, the carbohydrate and caloric content of the upcoming meal, and recent or planned physical

activity. CSII therapy has demonstrated more flexibility, better glycemic control, and less hypoglycemia compared with intensive insulin therapy.<sup>13</sup> However, data are not currently available on the effect of CSII therapy on complications related to diabetes. Both insulin aspart and lispro are compatible with infusion pumps and have a better bolus action than regular insulin because of their more rapid subcutaneous absorption.<sup>14,15</sup>

The use of this strategy is not suitable for all patients. It is best for patients who are motivated, mechanically adept, educated about diabetes, and willing to monitor blood sugars. The most important predictor of

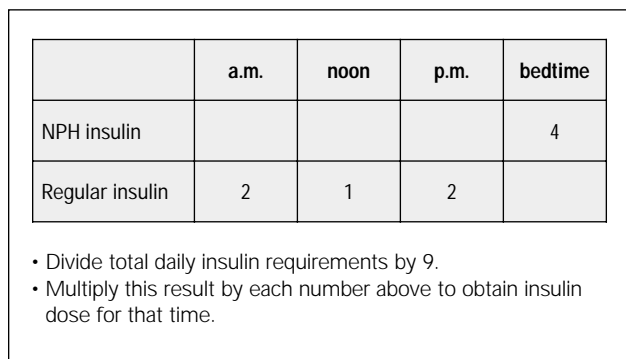


Figure 3. How to start MDI: "Rule of 9."

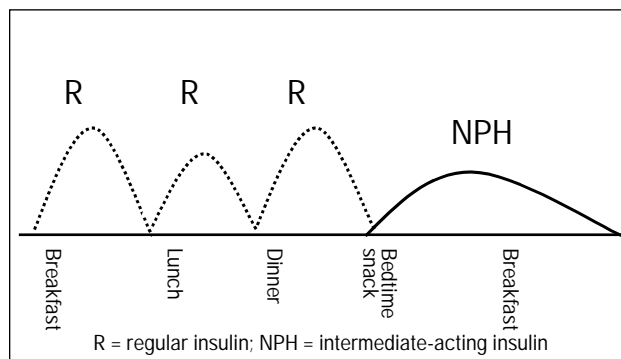


Figure 4. Insulin action profile for "Rule of 9."

success is the insulin pump user's willingness to learn and apply aggressive self-care measures. Frequent monitoring of blood sugars is the only method by which pump failure can be detected and corrected before life-threatening ketoacidosis ensues. Known complications include skin infection (approximately once every 27 patient months) and ketoacidosis (approximately once every 78 patient months), which can rapidly occur if insulin delivery is interrupted.<sup>16</sup> The pumps and pump supplies are also costly and may not be affordable for all patients with diabetes.

### Self-adjustment of insulin dosing

Traditionally, health care providers aimed to train people with diabetes to use assigned fixed doses of insulin and to follow a fixed meal schedule to fit the insulin regimen. In other words, patients were asked to change their life to meet the demands of the insulin action, or else face the consequence of high or low blood sugars. Patients would habitually report results of home blood glucose monitoring to nurses and physicians, who would then recommend insulin doses and meal plans. This took away the control of diabetes from the patient and placed rigorous demands on their lifestyle that were often not realistic or attainable.

In this day and age, the means by which optimal glycemic control can be achieved should be controlled by the patient. As health care providers, we should aim to help patients become expert in the use of variable doses of insulin. By providing the necessary tools, assistance, and knowledge, we can empower patients with diabetes, allowing them to improve their own glycemic control and take responsibility for insulin adjustment in a way that best suits their lifestyles.

**Step 1: Set a basal rate**

- Determine pre-CSII total daily insulin dose.
- Determine the new total daily insulin dose (75% of pre-CSII daily insulin dose), e.g., 64 U / x 75% = 48 U
- Divide by 2, then divide by 24 (hours in the day) to determine the estimated hourly basal rate, e.g., 48 U/2 = 24; 24 U/24 = 1 U/h
- Use this as a basal rate to start.
- Prepare to adjust basal rate subsequently as needed.

**Step 2: Determine meal bolus amount**

- Determine the insulin-to-carbohydrate ratio. (The insulin-to-carbohydrate ratio guides how many units of insulin are required for a given amount of carbohydrate intake.)
- Method 1. Insulin-to-carbohydrate ratio = Total grams of carbohydrate consumed in 1 day divided by 50% of the new total daily insulin dose, e.g., 240g/24 U = 10 grams/U
- Method 2. "500 Rule." Insulin-to-carbohydrate ratio = 500 divided by current total daily insulin requirement, e.g., 500/48 U = 10 grams/U
- Take 1 unit of insulin for every \_g of carbohydrate. Using the previous example, this would mean taking 1 U of insulin for every 10 g of carbohydrate consumed.

**Step 3: Be prepared to correct high blood sugars**

- Give a correction bolus for blood sugars >10 mmol/L.
- Calculate the correction bolus:  

$$\frac{\text{Measured glucose value} - \text{Desired glucose value}}{\text{Insulin sensitivity factor}}$$
- The insulin sensitivity factor is the amount that 1 U of rapid-acting insulin will lower blood glucose and is calculated as follows:  

$$\text{Insulin sensitivity factor} = 100 \text{ divided by new total daily insulin dose, e.g., } 100/48 = 2$$
 Administering 1 U of insulin can thus be expected to lower the blood glucose by 2 mmol/L.
- The correction bolus for a high sugar with positive ketones is larger than the usual one as extra insulin is needed to reverse ketosis:  

$$\frac{\text{Measured glucose value} - \text{Desired glucose value} \times 1.5}{\text{Insulin sensitivity factor}}$$

Figure 5. How to start CSII therapy using an insulin pump.

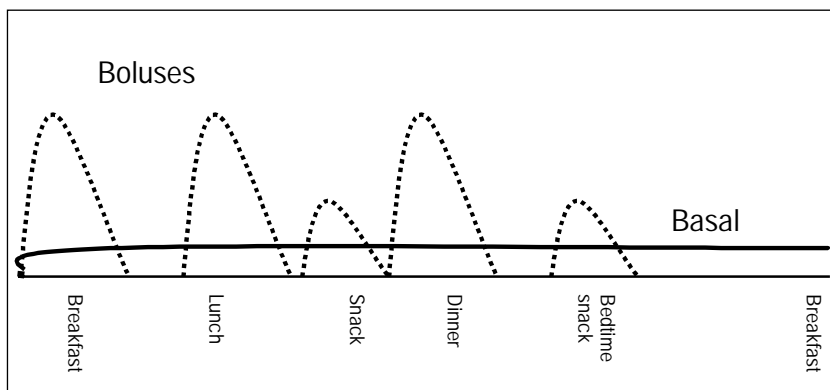


Figure 6. Insulin action profile for CSII.

## Conclusions

Advances in treatment regimens, insulins, and new devices have resulted in increased options and flexibility in the treatment of type 1 diabetes. Insulin analogs are now able to more closely mimic physiological insulin secretion and thus achieve better glycemic control in patients with diabetes. Moreover, insulin analogs have been shown to reduce the frequency of hypoglycemia. The increase in options for patients with diabetes over the past decade is helping achieve the ultimate aims of physiological insulin replacement and the prevention and reduction of diabetes-related complications.

### Competing interests

None declared.

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