Optimizing the Treatment of Type 2 Diabetes Using Current and Future Insulin Technologies

As the prevalence of type 2 diabetes increases due both to the growing prevalence of obesity and the increasing number of patients living longer, the number of people needing insulin therapy is expected to rise greatly over the coming years. The growth of this patient population has serious implications for surgical departments because diabetes predisposes patients to conditions requiring surgery, such as coronary artery bypass (CABG) and amputations due to peripheral vascular disease (Clement, Braithwaite et al., 2004).

Tight glycemic control is of particular importance in patients with diabetes undergoing operational procedures, as it has a significantly beneficial impact on morbidity and mortality (Clement, Braithwaite et al., 2004). Numerous studies have shown that hyperglycemia is associated with poor outcomes in a variety of clinical settings (Clement, Braithwaite et al., 2004; Dronge, Perkal, Kancir, Aslan, & Rosenthal, 2006).

In patients with diabetes who undergo CABG, for example, risk of death increases by 17% for every 1 mmol/L (18 mg/dL) increase in average glucose level above 6 mmol/L (108 mg/dl) (McAlister, Man, Bistritz, Amad, & Tandon, 2003). In patients undergoing cardiac and non-cardiac surgery, glycated hemoglobin (HbA1C) levels less than 7% were associated significantly with a decrease in infectious complications (Dronge et al., 2006). The Portland Diabetic Project in cardiac surgical patients found that blood glucose levels were associated strongly and independently with length of stay; each decrease of 77 mg/dL was associated with a saving of 1 day (Furnary, 2006). While IV insulin usually is recommended for glycemic control during surgical procedures (Clement, Braithwaite et al., 2004), most of the supporting studies were conducted before the availability of rapid-acting analogs which can provide good control following subcutaneous administration (Rhodes, Ferrari, & Wolfsdorf, 2005).

The fact that hyperglycemia is associated with poor inpatient outcomes should make good glycemic control a high priority, so patients with diabetes are not disadvantaged unnecessarily if they require surgery. Barriers to the optimum use of insulin unfortunately remain, such as fear of hypoglycemia and perceived complexity. Nurses and nurse practitioners occupy important positions in the diabetes care team, especially regarding patient education about advances in insulin therapy. Recent developments in insulin technologies that can contribute to overcoming barriers, and thus help to achieve optimum glycemic control in patients with type 2 diabetes who require insulin therapy, are identified.

Early Intervention

While national and international guidelines for type 2 diabetes vary slightly (see Table 1), they generally agree that HbA1C results ideally should be as close as possible to the range found in nondiabetic individu-
If lifestyle interventions and anti-diabetic agents fail to achieve these levels, insulin should be introduced (American Diabetes Association [ADA], 2008; Nathan et al., 2006; National Institute for Clinical Excellence [NICE], 2002). However, insulin can be used in the early stages of type 2 diabetes in appropriate patients and is considered the most effective treatment for lowering extremely high glucose levels (>8.5% HbA1C) (ACE/AACE Diabetes Road Map Task Force [ACE/AACE], 2006; ADA, 2008). Early and intensive insulin therapy now is recognized as a valuable treatment option in type 2 diabetes, as the potential for improved glycemic control that it offers could help reduce diabetes-related complications (Palumbo, 2004; UK Prospective Diabetes Study Group, 1998). Newer insulin formulations and delivery devices should make it easier for insulin to be introduced and accepted at an earlier stage in routine medical practice.

### Insulin Analogs

The introduction of insulin analogs (see Table 2) has improved the management of diabetes greatly because they more closely mimic the effect of endogenous insulin than do administered human insulins (Brunton et al., 2005; Hirsch, 2005). In basal-bolus insulin analog therapy, a long-acting insulin analog supplies the basal insulin while rapid-acting formulations are given at meal times (i.e., prandial doses) to deal with the subsequent large increases in blood glucose (Brunton et al., 2005).

![Figure 1. Representative Time-Action Profiles of Insulin Analogs, Regular Human Insulin, and Premixed Insulin Analogs](image)

Adapted with permission from Brunton et al., 2005.

<table>
<thead>
<tr>
<th>Insulin Analog</th>
<th>U.S. Trade Name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-Acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td>NovoLog®</td>
<td>Novo Nordisk, Bagsvaerd, Denmark</td>
</tr>
<tr>
<td>Lispro</td>
<td>Humalog®</td>
<td>Eli Lilly, Indianapolis, IN</td>
</tr>
<tr>
<td>Glulisine</td>
<td>Apidra®</td>
<td>Aventis Pharma SA, Antony, France</td>
</tr>
<tr>
<td><strong>Long-Acting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td>Levemir®</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td>Glargine</td>
<td>Lantus®</td>
<td>Sanofi-Aventis, Frankfurt, Germany</td>
</tr>
<tr>
<td><strong>Premixed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% aspart protamine/30% aspart</td>
<td>NovoLog® Mix 70/30</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td>75% lispro protamine/25% lispro</td>
<td>Humalog® Mix75/25™</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>50% lispro protamine/50% lispro</td>
<td>Humalog® Mix50/50™</td>
<td>Eli Lilly</td>
</tr>
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</table>

### Table 2. Summary of Insulin Analogs

- **Insulin Analog**
  - **U.S. Trade Name**
  - **Manufacturer**
- **Rapid-Acting**
  - Aspart: NovoLog®
  - Lispro: Humalog®
  - Glulisine: Apidra®
- **Long-Acting**
  - Detemir: Levemir®
  - Glargine: Lantus®
- **Premixed**
  - 70% aspart protamine/30% aspart: NovoLog® Mix 70/30
  - 75% lispro protamine/25% lispro: Humalog® Mix75/25™
  - 50% lispro protamine/50% lispro: Humalog® Mix50/50™

**Clinical Excellence [NICE], 2002.**
Insulin detemir has a less variable effect on blood glucose within individuals than insulin glargine or NPH insulin, and causes less weight gain than NPH insulin (Heise et al., 2004; Home & Kurtzhals, 2006).

Premixed formulations contain rapid-acting and intermediate-acting analogs in the same vial or device. Compared with premixed formulations of human insulins, analog premixes have a more rapid onset of action and greater lowering of post-prandial glucose (PPG), and can be dosed within 15 minutes of meal times (Davidson, Vexiau, Cucinotta, Vaz, & Kawamori, 2005; Garber, 2006). Because analog premixes address basal and prandial insulin needs in a single injection, they may reduce the number of injections required. Patients can start with once-daily dosing and increase the frequency as necessary up to three times daily (Garber, 2006). Insulin aspart 70/30 plus metformin (Glucophage®) given twice daily proved to be an effective initial therapy in a study of 58 patients; mean HbA1C decreased from 10.8% to 5.9%, with all patients achieving a result less than 7% (Lingvay, Hendra, 2006). Insulin aspart 70/30 plus metformin (Glucophage®) given twice daily proved to be an effective initial therapy in a study of 58 patients; mean HbA1C decreased from 10.8% to 5.9%, with all patients achieving a result less than 7% (Lingvay, Hendra, 2006).

Table 3. Advantages of Available Delivery Systems

<table>
<thead>
<tr>
<th>Device</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefilled (disposable) pen (e.g., FlexPen® [Novo Nordisk, Bagsvaerd, Denmark]; Humalog® [Eli Lilly, Indianapolis, IN], SoloSTAR® [Aventis Pharma, Frankfurt, Germany]; KwikPen® [Eli Lilly, Indianapolis, IN])</td>
<td>Compact, discreet, patient preferred</td>
</tr>
<tr>
<td>Reusable (durable) pen (e.g., HumaPen® LUXURA® [Eli Lilly, Indianapolis, IN], NovoPen® [Novo Nordisk, Bagsvaerd, Denmark], OptiClick® [Aventis Pharma, Frankfurt, Germany])</td>
<td>Compact, discreet, patient preferred</td>
</tr>
<tr>
<td>Prefilled doser (e.g., InnoLet® [Novo Nordisk, Bagsvaerd, Denmark])</td>
<td>Easy to use</td>
</tr>
<tr>
<td>Insulin pump</td>
<td>Most accurate dosing</td>
</tr>
<tr>
<td>Jet injectors</td>
<td>Needle-free</td>
</tr>
</tbody>
</table>


The choice of insulin formulations and delivery devices can be influenced by many factors, such as level of glycemic control (including HbA1C fasting plasma glucose and PPG levels), disease duration, lifestyle, vision, hearing, and dexterity (Cooppan, 2007; Hendra, 2002). Once insulin treatment is required, patients usually have basal insulin added to their oral hypoglycemic agents, although premixed insulins are also an option when initiating insulin. Blood glucose targets are set and the insulin is titrated in 2-3 unit increments every 2-3 days until glycemic goals are attained or hypoglycemia occurs. Patients are introduced gradually to a basal-bolus regimen when necessary (Meneghini, Rosenberg, Koenen, Merilainen, & Luddeke, 2007). Frequency of blood glucose monitoring also should be considered when initiating insulin therapy (AACE Diabetes Mellitus Clinical Practice Guidelines Task Force, 2007; ADA, 2008).

Delivery Systems

Injection has been the primary method used to deliver insulin for over 80 years. Inhaled insulin for meals became an option only in 2006. Insulin jet injectors, although they have been available for many years, rarely are used (Cefalu, 2004; Lenzer, 2006).

While today’s syringes are smaller and have finer needles and special coatings to make injection easier, some patients still experience psychological and physical problems with them (Meece, 2006). Numerous devices are available to make insulin administration easier for patients with diabetes; a summary of these, with their key advantages, is shown in Table 3.

Insulin pens can reduce the complexity and stigma of insulin administration. They are not only convenient and easy to transport, but also unobtrusive to use (Stewart, 2004). Pens were preferred to syringe injection by 75%-90% of patients in crossover studies to compare delivery methods (Flood, 2006; Rubin & Peyrot, 2004). In an audit of patients who were switched from oral medication to insulin therapy using injection pens, most patients stated that they wished they had initiated insulin earlier, and would have...
done so had they known that injection was so easy (Da Costa, Brackenridge, & Hicks, 2002; Graff & McClanahan, 1998; Korytkowski, Bell, Jacobsen, Suwannasari, & FlexPen Study Team, 2003). As a result of their ease of use and high adherence rates, insulin pens can reduce insulin-related hypoglycemic events and more severe long-term complications, thereby improving patient quality of life and reducing hospitalizations and associated costs (Korytkowski et al., 2003; Lammert et al., 2006; Lee, Balu, Cobden, Joshi, & Pashos, 2006). In addition, pen adoption probably can reduce the number of home visits for injection assistance by making injections easier for partially disabled patients to manage independently.

An insulin pump is an option that is being used increasingly by patients with type 2 diabetes. Insulin pumps provide continuous subcutaneous insulin infusion (CSII) using a single type of insulin (either a rapid-acting insulin analog or regular human insulin) to address both basal and prandial insulin requirements. CSII closely mimics the normal physiology of insulin secretion because the pump can be programmed to give various basal rates with bolus dosing as needed; all adjustments are based on need, which is assessed by blood glucose monitoring. In this way, CSII mimics the way the pancreas meets basal and prandial insulin needs with a single type of insulin (endogenous insulin) (Kirk, 2003). The MiniMed Paradigm® REAL-Time System (Medtronic MiniMed, Inc, Northridge, CA) is the first insulin pump with an integrated continuous glucose monitoring system, and thus represents another step toward artificial pancreas technology.

Jet injectors are needle-free devices that deliver insulin by a high-pressure stream into the subcutaneous tissue. However, they are not used commonly because they can cause bruising at the injection site; in addition, some patients find them more uncomfortable than conventional injections. While jet injectors can benefit patients with genuine needle phobia or severe insulin-induced lipoatrophy (ADA, 2003; Cefalu, 2004), they should not be seen as a routine option.

The first insulin inhalation (Exubera®), a powdered insulin formulation, was thought to be a way to encourage earlier initiation of insulin therapy among patients who were reluctant to accept injections. However, it was a rapid-acting insulin that therefore provided meal coverage but did not replace basal insulin, the most common way to initiate insulin. Insulin inhalation was contraindicated in smokers and those with pulmonary disease, and also was associated with a small, non-progressive decline in forced expiratory volume (McMahon & Arky, 2007). It did not gain acceptance and was withdrawn from the U.S. market in 2007 due to low adoption rates and poor sales (Johnson, 2007). However, other inhaled insulins are still in clinical development (see Table 4).

**Reassuring Patients about Insulin Therapy**

Insulin analogs help to address three key patient concerns: they are less likely to cause hypoglycemia than comparable human insulins, more convenient to dose and, in the case of insulin detemir, less likely to cause weight gain (Home & Kurtzhals, 2006). Also, as the fear of hypoglycemia subsides, patients may be less susceptible to weight gain due to defensive snacking.

The increase in dosage accuracy and patient acceptability associated with pen devices (see Figure 2) should help patients adhere to their insulin regimens and thus contribute to better glycemic control. Many patients still think that insulin administration is complex and disruptive. The new insulin analogs allow insulin regimens to suit almost every lifestyle. For example, because rapid-acting analogs can be given immediately before a meal, they are useful to people with unpredictable eating patterns. Premixed formulations reduce the need for multiple injections because they usually need to be given only twice a day. Modern delivery devices can make administration very easy, allowing discretion and reducing potential embarrassment in social, holiday, work, or school situations (Meece, 2006).

Despite improvements in needles that may allow less painful administration of insulin than previously, some people still have difficulty with self-injection. The pen devices help to overcome this difficulty because they do not look like syringes typically used for injections. They also may cause even less discomfort than the standard syringe/needle combination because pen needles often are shorter and available in finer gauges. Automatic needle shields (e.g., NovoFine® Autocover® [Novo Nordisk, Bagsvaerd, Denmark]; AUTOject® 2 [Owen Mumford Ltd, Oxford, UK]; Inject Ease® [Palco Laboratories, Santa Cruz, CA]) are available for some pen devices. These shields hide the needle, but allow it to be pushed through the skin at the touch of a button. In addition, they help to prevent accidental needlesticks. Patients with genuine needle phobia can be considered as candidates for jet injectors (Brunton, Davis, & Renda, 2006; Campbell & White, 2002; Meece, 2008).

Some patients think insulin is a last resort and they have failed in their disease management if insulin is prescribed. Owing to the progressive nature of the disease, most patients with type 2 diabetes eventually will need insulin (Brunton et al., 2005). However, physicians and other health care providers may be more likely to consider the introduction of insulin at an earlier stage than previously in view of the more physiological time-action profiles of the new insulin analogs, the generally reduced risk of hypoglycemia, and the flexibility with which new medications can be administered. Earlier introduction of insulin should help convince patients that insulin treatment is a positive option and not a punishment for failure (Choe, Edelman, 2007; LeRoith, Levetan, Hirsch, & Riddle, 2004; Spellman, 2007).

Because insulin often has been introduced after diabetes has advanced and complications have developed, patients may think that insulin itself can cause complica-
tions and death. They instead should be taught that poor glycemic control (not insulin) is responsible for complications, and then reassured that the new insulin analogs, together with modern delivery devices, can help provide the tight glycemic control required to reduce the possibility of diabetes-related complications (Palumbo, 2004; Spellman, 2007).

The number of elders and children with type 2 diabetes is increasing. Both these patient groups may be in particular need of reassurance about initiating insulin therapy.

### Older Adults

The highest prevalence of type 2 diabetes is among older patients; in 2005 the prevalence of diagnosed diabetes among people ages 65-74 was about 12 times that of people less than age 45 (Centers for Disease Control and Prevention, 2007). Because type 2 diabetes is likely to be more advanced in older adults than in their younger counterparts, they may not be able to achieve adequate glycemic control without insulin (Cefalu & Cefalu, 2007).

When initiating insulin in elders, the health care provider must take many factors into consideration, including co-morbidity and associated polypharmacy, cognitive function, level of independence, and anticipated onset of frailty (Hendra, 2002). Most older adults starting insulin can self-inject, and results with basal-bolus regimens can be as good as in younger patients (ADA, 2008; Cefalu & Cefalu, 2007; Hendra, 2002).

The risk of hypoglycemia is a particularly important consideration in elders, especially for persons who live alone, take multiple medications, or have been hospitalized recently (Cefalu & Cefalu, 2006). In the general population, the use of insulin analogs can reduce the incidence of hypoglycemia, including nocturnal hypoglycemia, compared with NPH insulin (Davidson et al., 2005; Peterson, 2006). Many older adults starting insulin can self-inject, and results with basal-bolus regimens can be as good as in younger patients (ADA, 2008; Cefalu & Cefalu, 2007; Hendra, 2002).

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The short, fine needles also are less painful, and therefore suitable for thin skin. The InnoLet® prefilled doser (Novo Nordisk, Bagsvaerd, Denmark) further facilitates self-injection by visually and physically impaired persons, thereby reducing the need for home care visits for injection assistance (Shelmet et al., 2004).

### Future Developments in Insulin Delivery

<table>
<thead>
<tr>
<th>Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled (Flood, 2006)</td>
<td>Insulin inhalation (Exubera®) withdrawn from U.S. market; other formulations in development, e.g. AERx insulin Diabetes Management System (Aradigm Corp, Hayward, CA/Novo Nordisk, Bagsvaerd, Denmark), Aerodose insulin inhaler (AeroGen Inc., Sunnydale, CA).</td>
</tr>
<tr>
<td>Oral enteric (Flood, 2006)</td>
<td>Capsule formulations of insulin currently are undergoing clinical trials.</td>
</tr>
<tr>
<td>Intranasal (Flood, 2006)</td>
<td>Both liquid and powder systems are being evaluated. Absorption enhancers may irritate the mucosa and nasal congestion may decrease availability.</td>
</tr>
<tr>
<td>Closed-loop implantable devices (Hanaire, 2006)</td>
<td>Will operate as an “artificial pancreas,” with a continuous glucose sensor and automatically adjusted insulin doses.</td>
</tr>
<tr>
<td>Transdermal (Flood, 2006)</td>
<td>Iontophoresis or low-frequency ultrasonic transmissions move the insulin molecule across the skin.</td>
</tr>
<tr>
<td>Oral buccal (Flood, 2006)</td>
<td>Oral aerosolized sprays of liquid insulin are currently in development.</td>
</tr>
<tr>
<td>Biotechnology (D’Anneo et al., 2006; Gangaram-Panday, Faas, &amp; de Vos, 2007)</td>
<td>The possibility of implanting genetically engineered β-cells or embryonic stem cells, as well as gene therapy (introduction of the insulin gene into any cell in the body), is under investigation.</td>
</tr>
<tr>
<td>Pancreatic transplantation (Witkowski, Zakai, Rana, Sledzinski, &amp; Hardy, 2006)</td>
<td>Although technology has improved dramatically, it is not performed widely (about 15,000 patients worldwide). Requires lifelong immunosuppressant therapy.</td>
</tr>
</tbody>
</table>
over age 65, the ADA (2008) recommends that older adults with diabetes be treated to the glycemic goals stated for younger adults if they have a life expectancy of greater than 10 years, are active, have good cognitive function, and are willing to self-manage. Less-aggressive glycemic goals are proposed for persons with cognitive or functional impairment, and/or those who are frail and have advanced diabetes complications.

Children

The disturbing rise in the number of children and adolescents with type 2 diabetes means that they will be admitted increasingly for surgical procedures. As with adult patients, tight glycemic control is crucial to successful outcomes (Rhodes et al., 2005).

Outside the surgical setting, rapid-acting analogs are suitable for some children as they can be given immediately before meals and so fit in with irregular eating patterns more easily than regular human insulin. By contrast, use of premixed insulins avoids the need for injections during school hours; however, these formulations do not always provide sufficient insulin to cover lunch time needs. A growing number of children, especially adolescents and pre-adolescents, are adopting insulin pumps. These devices, which use rapid-acting analogs, are highly adaptable to dietary changes and high levels of activity. With experience and training in calculating carbohydrate loads at meal time, young patients can exert greater immediate control over their insulin requirements and therefore control their glucose more carefully (Copeland, Becker, Gottschalk, & Hale, 2005; Miller & Silverstein, 2005).

The Future

The future of insulin delivery is very exciting, with many novel treatments recently released or in development (see Table 4). A number of insulin delivery methods that do not require injection bear mention; these include oral buccal and intranasal for meal time coverage, and oral enteric and transdermal delivery for more sustained coverage (Flood, 2006).

Oral buccal preparations of recombinant human insulin now under development deliver an insulin solution in aerosolized form through the oral mucosa, with a reported onset shorter than that of injected insulin (Cernea, Kidron, Wohlgeleiter, Modi, & Raz, 2005; Guevara-Aguirre, Guevara, Saavedra, Mihic, & Modi, 2004). Delivery through the nasal mucosa is a related administration strategy that has demonstrated a 40-minute onset and potentially could be used to control meal time glucose excursions (D’Souza, Mutalik, Venkatesh, Vidyasagar, & Udupa, 2005).

An orally administered capsule formulation of insulin would allow absorption through the gastrointestinal tract, and could be easily accepted by patients; two different preparations currently are under development. One of these contains an insulin that has been modified to resist intestinal degradation and be absorbed in the portal circulation, while the other is formulated for intestinal absorption (Clement, Dandone, Still, & Kosutic, 2004; Kidron et al., 2004).

Transdermal drug delivery has been used for other types of drugs, and a number of methods are under consideration to optimize insulin administration by this route. One option is a patch with an ultrasonic device to dilate blood vessels in the skin, thus increasing the absorption rate compared with passive absorption (Smith et al., 2003). A second device generates a weak electrical current to promote electromigration as a means to achieve permeation (Batheja, Thakur, & Michniak, 2006). Additional methodologies under study are listed in Table 4.

Conclusions

The role of nurses as diabetes educators has become more important due to the increased incidence of type 2 diabetes. The development of new insulin analogs and modern delivery devices makes optimal glycemic control more achievable than ever before. These advances also demand more of nurses in terms of gaining familiarity and expertise with new technologies and treatment paradigms. Nonetheless, these developments will help nurses as members of the diabetes treatment team reassure patients who are about to begin insulin therapy.

References


