Evolving Trends in Insulin Delivery: In Pursuit of Improvements in Diabetes Management

Firas Akhrass, MD; Nancy Skinner, RN, CCM; Kimberly Boswell, MD; Luther B. Travis, MD

Diabetes mellitus affects 23.6 million Americans and its incidence is rapidly increasing, particularly in older, overweight patients. Large-scale studies conclusively show that elevated blood glucose levels are associated with an increased risk for microvascular complications, such as retinopathy and nephropathy. The high rates of morbidity and mortality associated with this disease, and the costs associated with it, underscore the importance of effective glycemic control. Conventional syringe/vial insulin delivery is associated with many barriers for patients with diabetes mellitus and for their healthcare providers. Substantial developments in insulin delivery show promise in overcoming these barriers. New technologies in insulin delivery focus on increasing patient convenience, reducing the frequency of daily injections, and improving glycemic control. This article outlines the challenges associated with conventional insulin delivery and describes recent developments that may help to overcome these barriers and, ultimately, could enhance glycemic control. [AHDB, 2010;3(2):117-122.]

Diabetes mellitus affects 23.6 million Americans, or about 8% of the US population. This includes nearly 18 million persons with diagnosed disease and about 5.7 million undiagnosed cases. The incidence of type 2 diabetes is rapidly increasing, particularly among older, overweight persons who have concomitant cardiovascular (CV) risks. The coexistence of diabetes mellitus and hypertension works synergistically to increase morbidity and mortality, especially renal and CV injury. Well-known, large-scale studies, such as the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study, conclusively show that elevated levels of blood glucose are associated with an increased risk of microvascular complications, such as retinopathy and nephropathy. The high rates of morbidity and mortality associated with diabetes, coupled with the costs of treating these sequelae, underscore the importance of effective glycemic control.

Maintaining optimal glucose control—defined by the American Diabetes Association as a glycosylated hemoglobin level of <7%—may require multiple daily insulin injections. However, conventional insulin injection techniques are a major cause of reduced patient adherence to treatment. Patient medication adherence and satisfaction with treatment regimens are more likely to occur with fewer medication side effects, as well as with reduced patient burden and inconvenience. Typical side effects of insulin therapy may include weight gain or hypoglycemic events.

Significant advances in insulin delivery have been aimed at improving patient convenience and enhancing glycemic control. Alternatives to syringe/vial insulin delivery include:

- Insulin pens
- Injection ports
- Insulin infusion pumps
- Transdermal insulin patches
- Inhaled insulin

Some of these methods, however, have not met with great success. Inhalable insulin was available in the United States from September 2006 through October 2007 but was subsequently withdrawn from the market because of poor utilization rates. Other advances currently in development include oral insulin and buccal insulin spray. An international phase 3 clinical trial is ongoing for both types of insulin delivery.

This article reviews the barriers to adherence to conventional therapy and evaluates developments in...
KEY POINTS

- Nearly 18 million Americans are diagnosed with diabetes, and about 5.7 million have the disease but have not been diagnosed.
- The high rates of morbidity and mortality associated with diabetes, and the costs associated with its treatment, underscore the importance of effective glycemic control.
- Conventional syringe/vial insulin delivery is associated with patient and physician barriers, such as psychological insulin resistance, patients’ fear of insulin side effects and complications, and required lifestyle changes/restrictions.
- Despite evidence that many patients with type 2 diabetes do not achieve glycemic control with oral therapy alone, some physicians are still reluctant to initiate insulin therapy.
- Developments in insulin delivery during the past 20 years have focused on increasing patient convenience and improved glycemic control.
- The newer insulin delivery modes include insulin pens, insulin injection ports, continuous subcutaneous insulin infusion pumps, transdermal patches, and inhalable devices.

the management of insulin-requiring diabetes that may help to overcome some of these barriers, as well as improve glycemic control and quality of life for patients with diabetes.

**Barriers to Conventional Insulin Injection Therapy**

**Psychological Insulin Resistance**

Psychological insulin resistance, defined as reluctance to initiate insulin injection therapy, is common among healthcare professionals and patients with diabetes mellitus. Despite ample evidence that many patients with type 2 diabetes do not achieve glycemic control with oral therapy alone, some physicians are still reluctant to initiate insulin therapy. Koro and colleagues found that despite frequent failure to achieve glycemic targets, the use of insulin declined from the 24% reported in the National Health and Nutrition Examination Survey (NHANES) III (1988-1994) to 16% in the initial release of NHANES IV (1999-2000), whereas the use of oral glucose-lowering monotherapy increased.

This may in part reflect the availability of more oral medications for diabetes, but it may also be the result of the perceived complexity and inconvenience of the therapeutic regimen, the belief that it is not effective in type 2 diabetes, and fears of hypoglycemic episodes and weight gain. In addition, clinicians may perceive that initiation of insulin therapy will require more practice resources than are readily available.

The relationship between psychological barriers to medication adherence and glycemic control can have important therapeutic implications. In a systematic literature review covering 1985 to 2007, Brod and colleagues evaluated 116 peer-reviewed articles to assess the impact of psychological insulin resistance on diabetes management. The investigators concluded that this phenomenon is affected by the following components:

- Patients’ beliefs and knowledge about diabetes and insulin
- Negative self-perceptions and attitudinal barriers
- Fear of side effects and complications of insulin use
- Lifestyle adaptations
- Restrictions required by insulin use
- Social stigma.

These factors may lead to delayed treatment initiation and compromised glucose control.

**Reduced Medication Adherence**

Decreased adherence because of injection-related anxiety can influence glycemic control and quality of life in patients with insulin-treated diabetes. Adherence to a daily regimen of multiple injections can be difficult to maintain, interfering with lifestyle, compromising optimal glycemic control, and potentially resulting in CV complications. In one study of elderly patients (aged ≥65 years) with type 2 diabetes who were treated in a managed care setting, an inverse correlation was observed between blood glucose-lowering medication adherence and healthcare service utilization (eg, emergency department visits, outpatient visits, hospitalizations). In this longitudinal cohort study, an increased medication possession ratio (MPR) for diabetes medications was the strongest predictor of decreased total annual healthcare costs: between 8.6% and 28.9% decrease in annual costs for every 10% increase in the MPR (P <.001).

**Alternative Modes of Insulin Delivery**

Insulin may have greater patient acceptance and reduced psychological impact when administered via an alternative (ie, non-vial/syringe) delivery mode. Newer routes of insulin delivery have been introduced over the years that may be more convenient and less traumatic than standard multiple daily injection therapy. There is sufficient evidence supporting patient preferences for modes of insulin delivery that result in ease of use, reduced fear/anxiety about insulin injections, and reduced fear of hypoglycemia. The evidence suggests that novel delivery systems improve medication adherence compared with conventional injection delivery and
### Table: Alternative Modes of Insulin Delivery

<table>
<thead>
<tr>
<th>Device</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin pen (replaceable cartridge and prefilled)</td>
<td>Discreet</td>
<td>Initially can be more expensive than vial/syringe</td>
</tr>
<tr>
<td></td>
<td>Injection may be more comfortable and less time consuming than vial/syringe</td>
<td>Cannot mix insulin types</td>
</tr>
<tr>
<td></td>
<td>Refrigeration not required</td>
<td>Some insulin is wasted</td>
</tr>
<tr>
<td></td>
<td>Easy to use</td>
<td>Possibility of air bubbles</td>
</tr>
<tr>
<td></td>
<td>Accurate dosing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disposable</td>
<td></td>
</tr>
<tr>
<td>Insulin injection port</td>
<td>Reduces need for multiple daily skin punctures</td>
<td>Possibility of crimping of device's soft cannula, resulting in limited medication delivery</td>
</tr>
<tr>
<td></td>
<td>May remain in place for 72 hrs before application of a new port</td>
<td>Possible skin irritation or failure of injection port adhesive patch</td>
</tr>
<tr>
<td>Insulin infusion pump (continuous subcutaneous insulin infusion)</td>
<td>Uses only rapid-acting insulin (most consistent profile)</td>
<td>Possibility of crimping of infusion set soft cannula, resulting in limited medication delivery</td>
</tr>
<tr>
<td></td>
<td>Accurate dosing</td>
<td>Possible skin irritation or failure of infusion set adhesive patch</td>
</tr>
<tr>
<td></td>
<td>Allows flexible lifestyle</td>
<td>Pump and supplies expensive</td>
</tr>
<tr>
<td></td>
<td>Closest to mimicking body's physiologic secretion of insulin</td>
<td>Undetected interruptions in insulin delivery may occur</td>
</tr>
<tr>
<td>Transdermal insulin patch</td>
<td>Reduces need for conventional needles</td>
<td>Requires high patient motivation, involvement, and commitment to use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Technology is new and costly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential damage to the skin must be more completely evaluated</td>
</tr>
<tr>
<td>Inhalable insulin</td>
<td>Need for fewer/no injections</td>
<td>Larger doses of insulin required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of patient/physician acceptance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary route not suitable for smokers or patients with asthma or other pulmonary problems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-term impact on lung structure/function not clear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasal route yields poor transport across nasal mucosa</td>
</tr>
</tbody>
</table>

can lead to enhanced glycemic control, patient satisfaction, and improved health-related quality of life.17,21,24

The alternative modes of insulin delivery are summarized in the **Table**. Various preparations of insulin and insulin analogs are available for these systems. Administration schedules usually combine types of insulin in a regimen specific to the individual needs of each patient in an attempt to mimic physiologic secretion of insulin.

**Insulin Pens**

The insulin pen device uses an insulin cartridge rather than a vial, as well as disposable needles. Pens are the predominant insulin delivery system in most of the world, except in the United States.25

The 2 types of insulin pens available are replaceable and prefilled cartridge. A replaceable cartridge pen reuses the pen portion. When the insulin is used up, the cartridge is replaced with a new cartridge. A prefilled pen is entirely disposable: when the insulin is gone, the pen is discarded.

The insulin pen was an important milestone in the delivery of insulin, because it is convenient, portable, and discreet. These characteristics are more accommodating to a patient’s lifestyle and may therefore improve quality of life. A randomized, open-label, crossover study was conducted at 50 physician offices in the United States.22 Patients completed several questionnaires, including the Insulin Device Preference Questionnaire. Among the entire cohort (N = 162), 72% of the patients indicated an overall preference for a disposable form of dosing (similar to an insulin pen) compared with 22% of those who preferred the vial/syringe (P < .001).22
Other advantages for pen users include convenience, ease of use, comfort associated with use in public and social settings, as well as decreased fear of self-injection. When multiple daily injections are required to reach recommended glycemic targets, pens may facilitate acceptance of such regimens, even when the increased frequency of injection is perceived to be a disadvantage.

Some insulin is wasted when pens are used: 1 to 2 units of insulin are lost when the pen is primed before each injection, and usually some insulin remains in the pen or cartridge (but not enough to inject) after use. Insulin pens do not permit mixing of insulin types; therefore, if the insulin mixture needed is not available as a premix, 2 injections must be given, 1 injection for each type of insulin.

## Pens are mechanically more complex and more costly than syringes and vials, with an annual cost between $2500 and $4500. However, these costs may be offset by decreased hospitalizations.

In addition, pens are mechanically more complex and more costly than syringes and vials, with an annual cost (of insulin and supplies) between $2500 and $4500. However, these costs may be offset by decreased hospitalizations. A recent study indicated that annual hypoglycemia-associated costs were reduced by $788 per patient (from $1415 to $627; P < .01), predominantly as a result of decreased hospitalization costs (from $857 to $288; P < .01). Annual diabetes-attributable costs were reduced by $600 per patient (from $8827 to $8227; P < .01).  

### Insulin Injection Ports

An insulin injection port is a novel, low-profile device that can reduce the impact of daily injections in adults and in children. This new technology offers a portal for delivering multiple doses of medication directly into the subcutaneous tissue without the need for multiple skin punctures.

The injection port is applied via a short insertion needle whereby a soft flexible cannula is guided into the subcutaneous space. Once applied, the insertion needle is removed, and only the soft, flexible cannula remains under the skin. A resealable medication port is directly atop the cannula and is kept in place on the skin’s surface with an adhesive pad. Through a standard insulin syringe or an insulin pen, the patient receives a dose of insulin given by injection through the port. Because the device can typically be worn for 72 hours, it can substantially reduce the number of daily skin punctures, because insulin is injected through the port rather than the skin. Potential application sites include the abdomen and thighs. Once instructed by a healthcare provider, patients can then self-apply the injection port.

Use of the injection port can result in relief of preinjection anxiety, injection problems, and the procedural pain of repeated injections. Reported side effects include erythema and possible skin irritation. Measures of glycosylated albumin were within equivalence analysis limits compared with standard injections (P = .99). The use of injection ports is not restricted to insulin. They can be used for other prescribed medications that require multiple daily subcutaneous injections. Indeed, the newer incretin mimetics, which mimic the effect of glucagonlike peptide-1, are injectable products that could be delivered in the same fashion.

### Continuous Subcutaneous Insulin Infusion Pumps

The continuous subcutaneous insulin infusion (CSII) pump, using a battery-powered pump, was introduced to treat type 1 diabetes more than 20 years ago. Rapid-acting insulins are appropriate for use in pumps. The CSII provides an approximation of normal plasma insulin profiles and increased flexibility regarding timing of meals and snacks compared with conventional insulin injection regimens.

Insulin pump therapy has been shown to result in improved metabolic control and reduced frequency of severe hypoglycemia. Pumps reduce the need for injections and are more adaptable to lifestyle modifications, such as delaying meals, variable sleep schedules, or variations in exercise patterns. Studies comparing CSII and multiple daily injections in patients with type 1 diabetes have shown outcomes (ie, improved glycemic control) that were comparable with or favored the former.

However, pumps are not necessarily discreet to use, and pump infusion sets may result in site infections, abscess formation, and scarring. They also require a high level of patient motivation and commitment. Furthermore, they are expensive, costing more than $5000 in initial costs (pump and supplies) and about $2500 to $4500 in subsequent annual costs. Proponents assert that insulin pump therapy produces long-term reductions in complications, which offset these costs. Cost-benefit may be realized primarily in patients with frequent episodes of hypoglycemia.

### Transdermal Patches

The insulin molecule is far too large to penetrate the skin passively. Therefore, active transdermal delivery systems have been developed that involve a chemical or mechanical disruption of the skin barrier. By using
an applied force, such as ultrasound or an electrical current, active transdermal systems can deliver large-molecule formulations through the skin and into the bloodstream.\textsuperscript{6} However, this technology is costly and still under development; before replacing conventional needles, the safety and efficacy of these patches in delivering insulin without damage to the skin must be more completely evaluated.

**Inhalable Insulin Devices**

The first inhaled version of insulin became available in September 2006 in the United States. However, this system failed to gain the acceptance of patients and physicians. Despite this product's failure, one company continues the development of inhalable insulin devices, and the United States may see a return of inhalable insulin to the market in the near future.

The bioavailability of inhaled insulin is less than 20%; therefore, dosage requirements and cost per treatment are increased in comparison with insulin administered by subcutaneous injection. In addition, the long-term effects of intra-alveolar insulin deposition and immunogenic safety of inhaled insulin have not been fully elucidated.\textsuperscript{17}

Delivery of inhaled insulin to the upper nasal airways suffers from poor transport across the nasal membranes. Delivery via this route requires very large doses of insulin or the use of a chemical to enhance insulin transport.\textsuperscript{16} Chemicals used to enhance insulin transport often cause nasal irritation and a runny nose. Underlying lung disease could disrupt the absorption of the intended insulin dose.

**Implications**

The increasing prevalence of diabetes worldwide is cause for concern, in terms of associated morbidity and increasing health costs. Insulin therapy is an integral part of the treatment of diabetes. The long-term benefits of insulin therapy to control blood glucose levels have been demonstrated in multiple clinical trials in patients with type 1 and type 2 diabetes mellitus.\textsuperscript{6,11,12} These studies demonstrated a correlation between tight glycemic control and a reduction in the progression of chronic complications associated with diabetes mellitus.

The insulin delivery mode is vital for its acceptance and adherence to therapy for achieving glycemic targets. Conventional multi-injection insulin delivery has been associated with perceived barriers on the part of patients and physicians. Substantial developments have occurred in insulin delivery during the past 20 years, focusing on increasing patient convenience and achieving better glycemic control to overcome barriers associated with conventional insulin injections.

**Conclusion**

Newer delivery devices may add a substantial upfront cost; however, the use of these devices to improve adherence could have significant implications on overall disease burden costs for patients and payers alike. These devices can also help to improve quality of life for patients with diabetes by reducing the number of daily skin punctures or providing enhanced convenience, and can help patients lead a life as normal as possible. In the long-term, cost-benefit analyses incorporating patient preferences would help gauge the cost-savings resulting from the use of these newer delivery devices.

**Acknowledgments**

This manuscript was supported by a grant from Patton Medical Devices, LP. The authors would like to thank Laurie Kozbelt for her editorial assistance with this manuscript.

**Disclosure Statement**

Dr Abdess is a Consultant to Patton Medical Devices and is on the Speaker’s Bureau of Amylin, AstraZeneca, Daiichi Sankyo, Forest, Lilly, and Takeda. Dr Boswell is a Consultant to Patton Medical Devices. Ms Skinner is a Consultant to Patton Medical Devices and is on the Advisory Board of Boehringer Ingelheim. Dr Travis is Co-chair of the Scientific Advisory Committee of and a Consultant to Patton Medical Devices.

**References**

15. Koro CE, Bowlin SJ, Bourgeois N, Felder DO. Glycemic control from 1988 to

**STAKEHOLDER PERSPECTIVE**

Diabetes: An Epidemic of Disastrous Proportions

**PAYERS/PROVIDERS:** Diabetes has become an epidemic of disastrous proportions in recent years. The aging and the fattening of Western populations in recent years have been associated with a tremendous amount of insulin resistance, which has led to the development of type 2 diabetes in many of the individuals who have a genetic vulnerability to this disease as a result of limited pancreatic reserve.

The vascular sequelae of diabetes are devastating in their impact upon morbidity and mortality. The microvascular complications include retinopathy, nephropathy, and neuropathy. The macrovascular complications include coronary artery disease, cerebrovascular disease, and peripheral arterial disease. Although patients with better control of their blood sugar levels suffer fewer vascular complications, it is extremely difficult to keep blood sugar levels in or near the normal range in a diabetic patient.

A very wide variety of factors can affect blood sugar levels, including diet, activity, and both physical and emotional stress. Even the most conscientious patients with diabetes experience an ongoing and very frustrating struggle to keep their blood sugar levels under control. Therefore, it is critical that there be as many options as possible available for the administration of the single most critical pharmaceutical agent in the treatment of diabetes—namely, insulin.

Diabetes is a state in which inadequate insulin effect manifests itself because of a severe deficiency of insulin secretion in the patient with type 1 diabetes, and because of a combination of inadequate insulin secretory reserve and the significant insulin resistance in the patient with type 2 diabetes. Therefore, the current update, by Dr Akhrass and colleagues, of the several delivery methods for insulin is very timely indeed.

**James V. Felicetta, MD**
Chairman, Department of Medicine
Chief, Medicine Service
Endocrinology and Metabolism Fellowship
Carl T. Hayden Veteran Affairs Medical Center, Phoenix, AZ