New Therapies for Type 1 Diabetes Mellitus

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Five to ten percent of patients with diabetes mellitus in the United States suffer from type 1 diabetes: approximately 1.5 million people. Type 1 diabetes occurs when there is no insulin production from the beta cells of the pancreas and has often been associated with younger patients and thin body habitus. Type 2 diabetes, often linked with obesity, is associated with impaired insulin secretion and insulin resistance. Although the therapeutic goal is to maintain strict glycemic control in both types, management of type 1 diabetes is of a dissimilar nature due to differences in pathophysiologic mechanisms and patient characteristics. Newer therapies are aimed at achieving better glycemic control with minimal compromise to lifestyle. Some of these treatment measures, such as insulin pump therapy, have been available for years but were not used frequently until the mid-1990s. The increased use of intensive insulin therapy became more readily acceptable after the Diabetes Control and Complications Trial showed a decrease in microvascular complications with better glycemic control (hemoglobin A1C value of 7% or less). Insulin pumps, along with meal timings and, to a certain extent, regulation of the amount of food consumed, have allowed diabetes patients a more flexible lifestyle. Newer insulins are structured to mimick the pharmacokinetics of the endogenous basal (peakless sustained activity) and bolus (short fast-acting) insulins. Development of continuous, noninvasive, glucose sensing devices may reduce the need for capillary blood glucose testing (needle pricks) and make diabetes management more patient friendly and effective.

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Type 1 diabetes leads to absolute insulin deficiency due to a genetically mediated immunologic destruction of the islet cells. The disorder affects 0.4% of people in the United States (1), and about 40% of those affected are younger than 20 years of age. Lifelong risk of close relatives of a type 1 diabetes patient developing the disorder is high: approximately 30% in monozygous twins, 6% in offspring, and 5% in siblings (2). The preclinical phase in a genetically predisposed individual is several years. Environmental insults such as food protein and viruses have been implicated as precipitating factors, but there is no definitive evidence to support this.

Affected patients need lifelong insulin treatment. Many patients are young, thin, and prone to diabetic ketoacidosis. Most (69%-74%) of affected individuals have anti-GAD (glutamic acid dehydrogenase) antibodies at the time of diagnosis (3). It has been conclusively shown in various studies that intensive glucose control reduces diabetes-related micro- and macrovascular complications (4-7).

Newer therapies for type 1 diabetes are aimed at developing insulin delivery systems that mimick normal physiology, identifying newer insulins that mimick endogenous insulin, and making blood glucose monitoring easy and painless. These include insulin pump therapy, newer insulins (glargine, aspart, and lispro), and the GlucoWatch®, a noninvasive glucose-sensing device. Finally, preventive strategies to limit immunologic injury and extend the preclinical phase for type 1 diabetes are being explored.

Insulin Pump Therapy

Insulin pump therapy (8) has been used since the early 1980s; however, its use has increased since 1993, when the results of Diabetes Control and Complications trial (DCCT) showed a marked reduction in the microvascular complications with intensive insulin treatment in type 1 diabetes (4). Despite these results, physicians are hesitant to use pumps because of the inherent ignorance of the technology, misconceptions regarding complications, and fear that

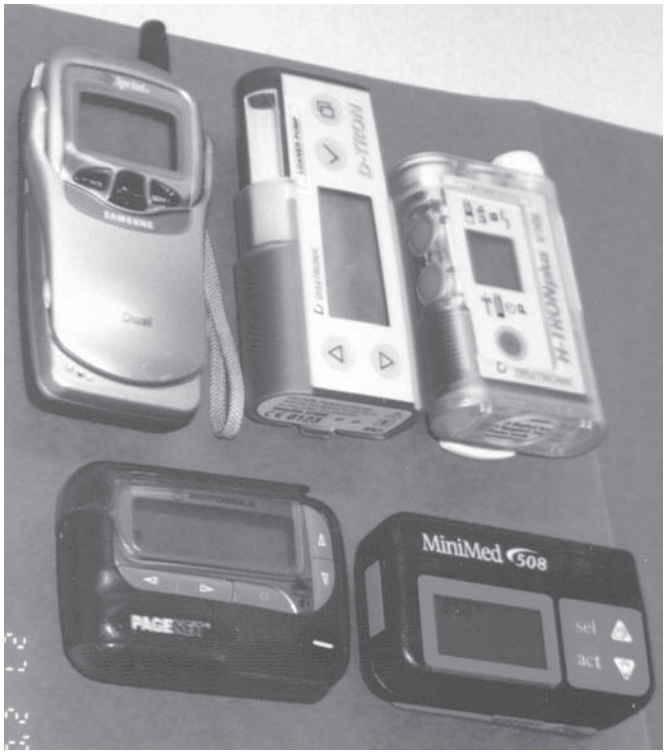


Figure1. The insulin pump is comparable in size to a cell phone or beeper. The cell phone in the upper left is similar to the Disetronic pump on the upper right. In the lower right corner, the MiniMed pump is comparable to that of a beeper on the left.

pumps will increase their workload. In fact, proper use of insulin pumps can improve blood glucose control; provide flexibility in lifestyle, meal timings, and amounts; and can lessen work to the physicians in the long run. However, insulin pump therapy requires a motivated patient who is willing to frequently self-monitor glucose levels.

How does the insulin pump work?

The insulin pump mimicks physiological insulin secretion. The normal pancreas secretes half of its insulin as a continuous basal secretion and half as meal-related boluses. Basal secretion controls the hepatic glucose output while the boluses control the postprandial hyperglycemia; the goal being to maintain the glucose in a normal range. An insulin pump is comparable in size to a beeper or cell phone (Figure 1) and can hold up to 300 units of insulin in its reservoir. A battery operated, computer chip-controlled plunger delivers continuous scheduled doses (programmed by the patient) of basal insulin from the insulin reservoir. The pump is connected to tubing, and a catheter is placed subcutaneously in the abdomen, thigh, arms, and buttocks. Basal insulin doses for various times throughout the day can be preset, and the patient can take calculated boluses prior to meals or snacks, as needed.

Table 1. Advantages of insulin pump therapy.

- Improved glycemic control and prevention of diabetes-related complications
- Fewer extreme blood glucose swings
- Better control of the "dawn phenomenon"
- Better control of hypoglycemic unawareness
- Flexible meal timing and lifestyle
- Less weight gain since less insulin is needed
- Improved growth and development in children

Table 2. Disadvantages of pump therapy.

- Diabetes ketoacidosis secondary to pump or tubing failure
- Cutaneous infections
- Cost
- Inconvenience of carrying around an attached device (and a constant reminder of diabetes)

Who are the candidates for pump therapy?

Pump therapy can be used in type 1, type 2, and gestational diabetes. A motivated person requesting pump therapy would be the ideal candidate. However, the patient should prove that he or she would be able to stay on an intensive regimen of multiple insulin injections and monitor blood glucose at least four times a day prior to starting on pump therapy. It is also indicated for people who have already been on intensive regimens that have not worked effectively, e.g. four or more injections a day. The pump works well for people who have a 'dawn phenomenon' or A.M. hyperglycemia. Hypoglycemic unawareness is another indication for pump therapy. Age is no barrier as long as the patient is functionally and cognitively intact. Pumps have been used in patients as young as 10 years of age. Insulin pumps are absolutely contraindicated in anybody with cognitive impairment or psychiatric illness. Medicare coverage for insulin pump therapy requires an undetectable C-peptide and is therefore covered only in type 1 diabetes.

What are the advantages of pump therapy? (Table 1)

Physiological: Most of the extreme swings of blood glucose in a conventional patient are due to erratic absorption and action of the subcutaneous injection of short- and intermediate-acting insulin. The insulin pump delivers short or rapid-acting insulin similar to endogenous insulin, causing fewer extreme swings of blood glucose.

Since it delivers insulin physiologically, less total insulin is needed and hence less weight gain occurs. Physiologic release of insulin can also improve residual beta cell function. Insulin resistance is high in the A.M. hours due to the increased levels of cortisol, growth hormone, and catecholamines. This causes the 'dawn phenomenon' or the A.M. hyperglycemia. The pump can be preset to increase the A.M. basal insulin infusion doses to offset the dawn phenomenon.

Lifestyle: Patients on pump therapy can be flexible with meal timing and amounts of insulin, though there is a misconception that initiating pump therapy means liberalizing meal consumption. On the whole, patients can be more flexible in eating habits, but optimal results are obtained when the patient calculates food and insulin doses.

Growth and metabolism: Pump therapy provides better glucose control and the prevention of chronic diabetes complications. With the total insulin decrease, there can be less increase in weight, and better blood glucose control improves growth and development in juvenile patients.

What are the disadvantages of pump therapy? (Table 2)

Pump failure can lead to very high blood sugar level and diabetic ketoacidosis. This is usually due to a kinking of the subcutaneous catheter or blockage in the tubing due to an air bubble. Patients should be taught to check the site and change the catheter and tubing for unexplained high blood sugars and should have a back-up insulin pen or bottles. Patients should also understand how to adjust the insulin when ill.

Cutaneous infection at the infusion site is generally due to prolonged use of the catheter at a single site. The catheter site needs to be rotated regularly (every 2-3 days). If the glycemic control is good, cutaneous infection tends to decrease.

Insulin pump therapy can also be expensive. Pumps alone can cost as much as $5500 initially, plus as much as $150 per month for supplies (catheter, tubings, glucose, ketostix strips). Most insurance companies cover at least 80% of the costs, but the process of obtaining insurance coverage can be time-consuming for the physician and staff.

The inconvenience of using a pump all the time can be a limited disadvantage. Patients will occasionally take a 'pump holiday,' taking a few days off the pump and going back to their intensive insulin regimen.

How to initiate pump therapy

Pre-pump education: Patients should meet with a team that includes a pump nurse or diabetes educator, dietitian, and physician to discuss targets of glycemic control. Patients should be given a pump to inspect and should be taught the mechanics of pump use including how to monitor and adjust the insulin for high and low blood glucose. Standard troubleshooting of the pump should also be explained. A dietitian should explain carbohydrate counting to determine their bolus doses; off-pump insulin regimen and sick-day rules should be made clear. A pump educator can teach most of this information.

Initiation: Insulin pumps are usually initiated on an outpatient basis. Generally, the pump educator gives a 2- to 3-day trial with normal saline infusion at home for the patient to adapt to the pump. Insulin lispro and highly buffered regular insulin are the only insulins to be used in the pump. Total dose is calculated by the amount of insulin a patient needs in 24 hours of his or her subcutaneous intensive regimen. This dose is cut by 25% (since patients on the pump need less insulin) and one-half of this dose is given as the basal insulin dose over 24 hours. (For example, if a patient is using 40 units of insulin a day, the total pump dose will be reduced by 25% to 30 units and the basal rate will be 50% of 30; i.e., 15 units, which is given over 24 hours at 0.6 units/hr). Basal insulin infusion rates usually vary two or three times a day to fit the blood glucose patterns over 24 hours and to offset the dawn phenomenon. The rest of the insulin is given as mealtime boluses with carbohydrate counting.

Common concerns and practical advice for the pump patient

The typical patient is anxious to find ways to cope with having an instrument on his or her body all day—and patients find ingenious ways to deal with the pump. Most wear their pump in a belt or pocket. For special occasions, they can wear it in a passport holder under the pants, in panty hose, or inside a specially designed bra. The catheter site can be disconnected for an hour for showering, exercising, swimming, or other activities. The pump is usually kept on a bedside stand during sleep and rarely causes problems during sexual intimacy. Patients can occasionally take a "pump holiday" but should be taught to begin their insulin regimens a few hours before turning the pump off to prevent a window with no insulin and exposure to hyperglycemia or even ketoacidosis. On vacations, patients should be reminded to protect the pump and insulin and themselves from sunlight and temperature extremes, which can cause disintegration of the insulin and enhance the absorption of injected insulin from the site, causing hypoglycemia.

Newer Insulins

Insulin is a 51-amino acid protein composed of an alpha and beta chain with a connecting peptide. Human insulin became available in 1979 when advances in genetic engineering helped to synthesize the first human insulin from *Escherichia coli*. Soon after, chemical substitutions to the terminal beta chain of the porcine molecule yielded human insulin (9). These developments led to the discovery of new, designer insulins. The first of these, insulin lispro (Humalog®, Eli Lilly & Company; Indianapolis, IN), was made by the reversal of the amino acid lysine for proline at positions 28 and 29 of the beta chain.

In the past year, the FDA has approved several new insulin analogs for human use. Glargine (Lantus®, Aventis; Strasborg, France) is a peakless, long-acting insulin that mimics basal insulin action. Aspart (NovoLog®, Novo Nordisk A/S; Bagsvaerd, Denmark) is a rapid-acting insulin similar to lispro. A stable premixed 75/25-lispro insulin (Humalog® mix 75/25) is available for better glycemic control. It is 75% long-acting NPL (a lispro analog similar to neutral protamine hagedorn [NPH]) and 25% lispro.

Glargine

Glargine is a peakless, long-acting insulin (duration 24 hours) that is synthesized by recombinant DNA technology. It is further chemically altered by substitution of two arginines with glycine at the 21 position of the alpha chain and two arginines added to the C-terminus of the beta chain. These changes make its hexamer structure more stable with less dissociation and slower absorption. Unlike other long-acting insulins, glargine is a clear solution with an acidic PH (of 4), which causes the formation of micro precipitate after injection that is slowly released in the circulation for 24 hours without a peak.

Six published studies of glargine (three in type 1, one in pediatric, and two in type 2) compared glargine (along with regular lispro or oral agents) with NPH and regular insulin, NPH and lispro, and NPH and oral agents (10). Study durations ranged from 16 to 52 weeks; four studies lasted 28 weeks. In all these studies, glargine significantly decreased the total insulin dose needed, with slightly better glycemic control that did not reach statistical significance. Pooled data from unpublished studies in the US and Europe show that the incidence of mild and severe hypoglycemia almost halved (16% vs. 30%, $P<0.05$, and 3% vs. 7%, $P<0.05$, respectively) in the glargine group (10,11).

Few adverse reactions were noted in glargine studies. Hypoglycemia occurred, but with reduced incidence compared with other agents (12). There was a higher incidence of transient injection site pain in glargine treated patients (2.7% vs. 0.7%). Glargine has not been studied in pregnant and lactating women. Like other long-acting insulins, it cannot be used intravenously.

Glargine provides new insights into diabetes management. Since it can be used as a basal insulin, patients with type 1 diabetes can take lispro with meals and glargine at bedtime—a scenario similar to pump therapy. This may be an alternative therapy to patients who refuse or hesitate to use pumps. However, glargine is not immune to pitfalls: its colorless formulation may allow for confusion with regular insulin; it may not have a perfect basal absorption in all patients; and it has to be taken separately from other insulins.

Aspart

Aspart is similar to lispro, a rapid-acting insulin analog formed by substitution of aspartic acid for proline at position 28 of the beta chain. This substitution prevents it from forming hexamer and, hence, causes faster absorption. Studies comparing aspart with regular insulin have shown that glycemic control was slightly better in the aspart group ($P<0.002$) with fewer hypoglycemic events but without statistical significance (13,14). In another trial of 90 type 1 diabetes patients, incidence of minor hypoglycemic events was similar, but the major hypoglycemic incidences needing assistance from others were significantly reduced in the aspart group ($p<0.02$) (15). Aspart can be used similarly to insulin lispro for glycemic control in type 1 or type 2 diabetes.

Insulin Pens

Insulin pens provide a compact and portable advantage for people with type 1 diabetes on multiple daily injections. Although they are easy to use, health care providers unfamiliar with the pens may be hesitant to teach patients about them. But once a patient has used a pen, he or she will not want to return to using the traditional bottles and syringe (16). Pens provide increased ease of use, accuracy, convenience, and less pain and fear of injections. Disadvantages are storage issues and increased cost over the conventional method. In Europe, 95% of those who require insulin use pens, while only 5% use them in the US. Government-funded health care systems may be the reason for the difference (17).

Regular insulin, NPH, lispro, NPH/ Regular 70/30 mixture, and a lispro mixture are available in pens. The lispro mixture is a newer FDA-approved insulin that has a 75/25 combination of lispro and NPL. It is available in a pen form and predominantly used for type 2 diabetes where glycemic control can be maintained with two insulin injections, similar to 70/30 (regular/NPH) combination. Glargine is also expected to be available in pen.

Glucose Sensing Techniques

Self-monitoring of blood glucose is critical in the management of diabetes. Intensive insulin regimens need extensive blood glucose monitoring that can be exhausting, painful, and require commitment by the patient. Currently available techniques are invasive, painful,

and do not provide continuous monitoring. It is worth noting that pharmaceutical companies are developing and producing less painful devices, like systems that use sites other than fingers, i.e. arms, legs. It would be extremely helpful to obtain a device that would be simple, noninvasive, and have the ability to provide continuous glucose sensing. Such devices could alert by an alarm when the blood glucose level falls below a threshold. Several devices are undergoing extensive research. One example of noninvasive monitoring, the GlucoWatch® Biographer (Cygnus, Inc; Redwood City, CA) (Figure 2) has been approved by the FDA and is available in Europe with possible marketing in the US this year.

The GlucoWatch® uses the principle of reverse iontophoresis, applying a constant, low-volt, electrical current through the skin, which causes migration of sodium and chloride to the cathode and anode on the device. A neutrally charged molecule such as glucose travels preferentially to the cathode where glucose is extracted from the skin and analyzed with an electrochemical enzymatic sensor.

The GlucoWatch® can be worn on the volar or dorsal surfaces of the forearm and is made up of a consumable transdermal pad called the AutoSensor and the Biographer monitoring device. It measures and displays glucose levels automatically, as often as every 20 minutes for up to 12 hours. It also creates an electronic diary, storing up to 4000 values that can be reviewed for patterns. Users can set personal glucose alert levels that sound alarms if readings are too high or too low.

One study comparing the GlucoWatch® to serial blood glucose measurements showed a good correlation between the readings (r=0.88; slope=1.03), though GlucoWatch® readings lagged behind approximately 20 minutes (18). Another study comparing GlucoWatch® to serial blood glucose monitoring in outpatient and home settings showed a strong correlation among values (r= 0.9; slope=1) (19). Based on the European and US data, the FDA approved GlucoWatch® with a preliminary letter in the Fall of 2000. It may be available commercially in 2001.

Figure 2. GlucoWatch®, worn on the forearm, is bigger than an ordinary watch. The Autosensor is located on the underside of the device and rests against the skin of the arm.

Advantages of GlucoWatch®:

- Noninvasive, automatic, and frequent measurements of glucose for 12 hours
- Alerts for high and low glucose levels
- Upward and downward trends indication
- Event markers to record seven different activities (e.g., meal, insulin)
- Discreet and portable

Pitfalls in GlucoWatch®:

- Use may be limited in patients with skin diseases
- Cost (of the watch-monitor, AutoSensor, and batteries)
- Not been studied in different races and skin colors
- New diagnostic tool – yet to be studied in different settings

Other Glucose Sensing Devices in Development

Several products are under development using a variety of technologies. Most focus on the development of painless sensing techniques (spectRx, Integ, Kumetrix). TCPI, Inc., for example, is designing a skin patch that is worn for 5 minutes to read glucose levels. For information on recent developments, several web sites are available, such as the Diabetes Mall (www.diabetesnet.com/sit.html).

Prevention of Type 1 Diabetes?

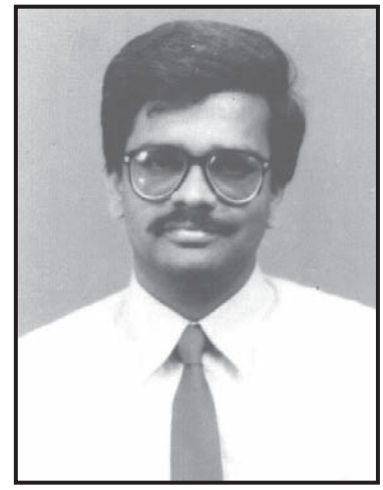
It is worth mentioning in passing that several studies have looked at ways to prevent type 1 diabetes and postpone immunologically mediated injury to the islet cells. Studies have been carried out with niacin and insulin injections in high-risk patients with elevated antiGAD antibodies (20). These agents have so far been disappointing in general. A complete review is beyond the scope of this article.

Conclusion

Complete insulin deficiency from loss of islet cell function leads to type 1 diabetes. Management is easier if the affected individual can "replace his brain for the functions of the pancreas"— adequate knowledge, understanding, motivation, and compliance are the primary necessities for the efficient management and prevention of chronic diabetes-related complications. Coupled with the patient's cooperation, a physician, nurse educator, and available technologies can help the patient to lead a more normal life. As health care providers, we should be able to identify these challenging patients and help them take control of their diabetes.

References

1. LaPorte RE, Cruickshanks KJ. Incidence and risk factors for insulin-dependent diabetes. In: National Diabetes Data Group. Diabetes in America: diabetes data compiled 1984. Bethesda, Md.: Department of Health and Human Services, 985:III-1-III-12. (NIH publication no. 85-1468.)
2. Atkinson MA, Maclaren NK. The pathogenesis of insulin-dependent diabetes mellitus. N Engl J Med 1994; 331:1428-1436.
3. Verge CF, Howard NJ, Rowley MJ, et al: Anti-glutamate decarboxylase and other antibodies at the onset of childhood IDDM: a population-based study. Diabetologia 1994; 37:1113-1120.
4. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329;977-986.
5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352: 837-853.
6. Hellman R, Regan J, Rosen H. Effect of intensive treatment of diabetes on risk of death or renal failure in NIDDM and IDDM. Diabetes Care 1997;20:258-264.
7. Okhubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103-117.
8. Fredrickson L, ed. The Insulin Pump Therapy Book; Insights from the experts. MiniMed Technologies, Sylmar, CA, 1995.
9. Goeddel DV, Kleid DG, Bolivar F, et al. Expression in Escherichia coli of chemically synthesized genes for human insulin. Proc Natl Acad Sci USA 1979; 76:106-110.
10. Lando HM. The New "Designer" Insulins. Clinical Diabetes 2000; 18:154.
11. Lantus prescribing information, Aventis Pharmaceuticals April 2000; Strasborg, France.
12. Ratner RE, Hirsch IB, Neifing JL, et al. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes Care 2000; 23:639-643.
13. Raskin P, Jovanovic L, Guthrie R, et al. Insulin aspart (Iasp) improves glycemic control compared to human insulin (HI) for patients with type 1 diabetes. Diabetes 1999; 48 (1 Suppl): A115S.
14. Home P, Lindholm A, Riis A. Improved long term control with insulin aspart versus human insulin in people with type 1 diabetes. Diabetes 1999; 48 (1Suppl): A358S.
15. Home PD, Lindholm A, Hylleberg B, et al. Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients. UK Insulin Aspart Study Group. Diabetes Care 1998; 21:1904-1909.
16. Robertson KE, Glazer NB, Campbell RK. The latest developments in insulin injection devices. Diabetes Educ 2000;26:135-138, 141-146, 149-152.
17. Fleming DR. Mightier than the syringe. Am J Nurs 2000;100:44-48.
18. Tamada JA, Garg S, Jovanovic L, et al. Noninvasive glucose monitoring: comprehensive clinical results. Cygnus Research Team. JAMA 1999; 282:1839-1844.
19. Garg SK, Potts RO, Ackerman NR, et al. Correlation of fingerstick blood glucose measurements with Gluco Watch biographer glucose results in young subjects with type 1 diabetes. Diabetes Care 1999; 22:1708-1714.
20. Vidal J, Fernandez-Balsells M, Sesmilo G, et al. Effects of nicotinamide and intravenous insulin therapy in newly diagnosed type 1 diabetes. Diabetes Care 2000; 23:360-364.



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