New Options in Insulin Pump Therapy

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The benefits of insulin pump therapy in patients with type 2 diabetes mellitus (T2DM) include flexibility, more physiologic and reproducible results and more predictable delivery of insulin. Philip Raskin, MD, University of Texas Southwestern Medical Center, Dallas, Texas, USA, outlined the current state of insulin pump therapy in T2DM.

Dr. Raskin presented data from a meta-analysis of 12 randomized, controlled trials comparing insulin pump therapy and multiple daily injection treatment in type 1 diabetes (T1D). These trials had a duration of 2.5 to 24 month, involved 301 patients, and demonstrated that insulin pump therapy resulted in a 0.51% decrease in HbA1C levels compared with multiple insulin injections [Pickup J et al. *BMJ* 2002]. The mean blood glucose concentration was decreased by 1.06 mmol/L, and patients who received insulin pump therapy required less insulin, with a dose reduction of 7.6 units/day. Thus in T1D it is easy to demonstrate an advantage to insulin pump therapy as compared to multiple daily injections.

However in T2DM it has been impossible to show a similar advantage. There are studies such as a prospective study of 21 patients with T2DM who had previously received multiple daily insulin injections, treatment with insulin pump therapy for 16 weeks resulted in a significant 1.2% decrease in HbA1C levels compared with baseline (p≤0.01) [Frias JP et al. *J Diab Sci Technol* 2011]. Patients reported they preferred insulin pump therapy over multiple daily injections (p≤0.001), and felt insulin pump therapy had greater clinical efficacy (p≤0.001). Patients also reported, however, that insulin pump therapy reduced their social burden and worries about their disease. However, in two randomized clinical trials comparing insulin pump treatment and multiple daily injections [Raskin P et al. *Diabetes Care* 2003] and [Herman WH et al. *Diabetes Care* 2005], it has been impossible to show a difference in HbA1C or hypoglycemic events between the two treatments (Table 1). In both of these studies which included >100 patients each, patients were randomized to either insulin pump treatment or multiple daily injections. HbA1C decreased in both treatment arms to the same degree. Hypoglycemia rates were the same. Of interest, in both studies patients preferred insulin pump treatment over shots. Because insulin pump treatment is more expensive than multiple daily injection and has no glycemic advantage Medicare will not reimburse for its use. That said, insulin pump treatment in T2DM is still a viable option for those who wish to use it, who are not on Medicare, and are able to afford it.

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Table 1. Comparison of Insulin Pump Therapy With Multiple Daily Injections in T2DM

	CSII		MDI	
	Baseline	**6 Months**	**Baseline**	**6 Months**
HbA1C	8.2±1.4	7.6±1.2	8.0±1.1	7.5±1.2
Δ HbA1C	—	−0.62±1.1	—	−0.46±0.9
Body weight (kg)	96.4±17	98.1±18.1	96.9±17.9	97.6±19.2
Hypoglycemic (% of subjects)	—	54	—	59
Rate (episode/subject)	—	0.8±1.6	—	1.2±3.1
Nocturnal (% of subjects)		16	—	22

CSII=continuous subcutaneous insulin infusion; MDI=multiple daily injection.

Howard C. Zisser, MD, Sansum Diabetes Research Institute, Santa Barbara, California, USA, presented information about pumps that are used in insulin pump therapy. Dr. Zisser pointed out that "one size doesn't fit all" and that as more pumps are released into the market, it is important to customize them to specific individuals.

A recent study demonstrated that a similar amount of insulin was released with a patch pump as with a traditional pump [Luijf YM et al *Diabetes Technol Ther* 2013]. One pump has a rechargeable pumping mechanism with short tubing and unique back-end software on a hand-held device with wireless connectivity, enabling patients to make changes, as required. Another company provides

patients with insulin data, exercise data, and food diaries at a central server that is accessible from anywhere. The JewelPUMP is a small microelectrical mechanical system that results in precise and consistent delivery of insulin. A hand-held unit, which is an Android cell phone with a unique SIM card, contains a meter.

The PaQ is a 3-day insulin pump with a reusable messenger unit that notifies patients when a new insulin pack is needed. A bolus dose of insulin can be administered by pressing a button. V-Go is an insulin pump that provides a preset basal rate, with the ability to give a bolus when needed. The Finesse pump has a preset bolus of 1 or 2 units.

A nonrandomized trial of 20 patients evaluated OmniPod, a pump that is widely available [Zisser H, Jovanovic L. *Diabetes* Care 2006]. After 30 days, the HbA1C levels decreased significantly compared with baseline, possibly because patients were never separated from their pumps, even while swimming or bathing. A subsequent study demonstrated that interruption from the pump, and therefore basal insulin, for 30 minutes resulted in a rise in blood glucose levels [Zisser H. *Diabetes Care* 2008].

Rubina A. Heptulla, MD, Albert Einstein College of Medicine, Bronx, New York, USA, discussed the use of combination infusions in the treatment of T1D. A major difficulty in the treatment of T1D is overall poor glycemic control, which may be related to factors other than insulin and diet, such as glucagon.

The β cell hormone amylin is secreted with insulin and has been found to be reduced in patients with T1D. It is thought to suppress glucagon secretion during the immediate postprandial period and to delay gastric emptying. In a study of 13 adolescents with T1D, patients received insulin monotherapy as the control or insulin plus a 24-hour subcutaneous infusion of pramlintide, a synthetic amylin analog [Heptulla RA et al. *J Clin Endocrinol Metab* 2009]. Patients who received pramlintide experienced reduced postprandial glycemic excursions as compared with patients in the control arm. However, pramlintide does not consistently normalize glucose excursions after meals [Weinzimer SA. *Diabetes Care* 2012].

The glucagon-like peptide 1 receptor agonist, exenatide, was originally developed for the treatment of T2DM. A dose-seeking study in 8 patients with T1D demonstrated that treatment with exenatide resulted in effective postprandial glucose lowering [Raman VS et al. *Diabetes Care* 2010]. In a subsequent comparison study, exenatide was demonstrated to be superior to pramlintide in decreasing blood glucose excursions. Dr. Heptulla concluded by suggesting the simultaneous infusions of glucagon and insulin with a bionic pump in a closed-loop setting is possible [Castle JR et al. *Diabetes Care* 2010].

Timothy S. Bailey, MD, San Diego, California, USA, discussed the safety and efficacy of low glucose (threshold) suspend technology. About a 2-hour period of hypoglycemia occurs before the onset of a hypoglycemic-induced seizure [Buckingham B. *Diabetes Care* 2008]. The Medtronic approach of low glucose threshold is that when blood glucose passes a threshold level, there is an immediate alarm. If the patient does not respond to the first alarm, a siren alarms.

A retrospective study demonstrated that the percentage of time that blood glucose levels were <50 mg/dL was significantly lower in patients who used the low glucose suspension mode, and that there was a significant decrease in the percentage of time that blood glucose levels were >240 mg/dL and 300 mg/dL [Agrawal P et al. *J Diabetes Sci Technol* 2011]. In a prospective, randomized trial, patients who exercised on a treadmill and used the low glucose suspension feature demonstrated glucose levels that were better maintained >70 mg/dL compared with patients who did not use the feature [Garg S et al. *Diabetes Technol Ther* 2012]. In an open-label, randomized, multicenter outpatient trial, patients with nocturnal hypoglycemia were randomly assigned to use the low glucose suspend feature or not [Bergenstal RM et al. *N Engl J Med* 2013]. The mean area under the curve for nocturnal hypoglycemia had a 37.5% relative reduction in patients that used the low glucose suspend feature compared with those who did not.

Many new types of pumps are available, from high-tech with customizable hand-held units to basic, simple units with preset functions. Many patients with T1D should be able to find an insulin pump that fits their personality and daily activities.