



# Insulin Pumps: Review of Technological Advancement in Diabetes Management



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## ABSTRACT

Insulin pump therapy, also known as continuous subcutaneous insulin infusion (CSII) therapy is an evolving form of insulin delivery which has been shown to be highly effective in maintaining euglycemia and providing patients with flexibility in their lives. It functions by providing the patient with a continuous subcutaneous infusion of a rapid acting insulin and allows the patient to administer boluses throughout the day for food and correction of high glucose levels. CSII is approved in patients with type 1 diabetes and selected patients with type 2 diabetes; however, it is important to select the right patients for pump therapy. Insulin pump technology continues to rapidly evolve, and many options are now on the market, including those that are used in conjunction with continuous glucose monitoring. This review article focuses on the pros and cons of CSII therapy as well as the technical and clinical considerations in starting a patient on this therapy.

**Key Indexing Terms:** Insulin pump; Continuous subcutaneous insulin infusion; Multiple dose injections; Diabetes mellitus; Hypoglycemia. [[Am J Med Sci 2019;358\(5\):326–331.](#)]

## INTRODUCTION

Current forms of insulin delivery used in the treatment of diabetes mellitus (diabetes) include disposable syringes, disposable or reusable pens and insulin pumps (also known as continuous subcutaneous insulin infusion [CSII] therapy). CSII therapy is a vital and evolving form of insulin delivery, which is mainly used by patients with type 1 diabetes (T1DM). Technological advances, software improvements and also widespread insurance reimbursement allow patients and clinicians unprecedented flexibility, improved glycemic control for patients, insight into the quality of diabetes control<sup>1</sup> and potentially reduced risk of chronic complications and premature mortality.<sup>2</sup>

## INSULIN PUMP VERSUS MULTIPLE DOSE INJECTIONS

The Diabetes Control and Complications Trial (DCCT) determined if people with T1DM kept their blood glucose levels as close to normal as safely possible with intensive diabetes treatment (3 or more insulin injections per day or an insulin pump with self-monitoring of blood glucose at least 4 times per day) they could slow the development of eye, kidney and nerve disease, compared to people who used the conventional treatment at the time of the study (1 or 2 shots of insulin per day with daily self-monitoring of urine or blood glucose). The mean

difference in hemoglobin A1c (HbA1c) levels between groups during the DCCT was about 2%. The DCCT ended after 10 years in 1993, with a mean of 6.5 years of follow-up of 1,441 adults and youth with T1DM, a year earlier than planned, as the study proved that participants who kept their blood glucose levels close to normal greatly lowered their chances of having eye, kidney and nerve disease. Major side-effects of intensive therapy were weight gain and increased risk of severe hypoglycemia.

The ongoing Epidemiology of Diabetes Interventions and Complications (EDIC) study, an observational follow-up to the DCCT, has continued to follow DCCT survivors for the last 20-plus years. EDIC has shown that there are long-term benefits of early and intensive blood glucose control on the future development of diabetes-related complications such as heart, eye, kidney and nerve disease. As shown by the DCCT/EDIC, early and intense blood glucose control reduces the risk of and slows the onset of the microvascular and macrovascular complications of diabetes for people with T1DM and leads to live longer and healthier lives. What was then intensive diabetes control is now the recommended standard care today. The pumps used today are more advanced than those used during the DCCT trial.

At the same time, multiple studies have suggested that persistent and severe hypoglycemia can increase cardiovascular morbidity and mortality,<sup>3</sup> which may

relate to cardiac arrhythmias and to proinflammatory, prothrombotic and endothelial dysfunction inducing effects of hypoglycemia.<sup>3</sup> CSII therapy has consistently been shown to result in lower HbA1c levels and decrease insulin requirements without increased risk of hypoglycemia when compared to multiple dose injections (MDI).<sup>4</sup> When a patient has frequent episodes of hypoglycemia, insulin pump use can reduce the frequency of hypoglycemia and beneficially raise HbA1c levels. Additionally, insulin pump therapy can provide a better quality of life, with more flexibility, and decreased incidence of hospitalizations and diabetes ketoacidosis (DKA) in the right patient population.<sup>5</sup>

In a meta-analysis of 23 randomized controlled trials (RCTs) comparing CSII to MDI, CSII users with T1DM had HbA1c levels that were on average 0.3% lower (95% CI -0.1 to -0.4).<sup>6</sup> OpT2mise was a multicenter study in which 331 uncontrolled patients with type 2 diabetes (T2DM) were randomized to either CSII or MDI. HbA1c reduced by 1.1 % in CSII compared to 0.4% in MDI ( $P < 0.0001$ ).<sup>4</sup> Berthe et al randomly assigned patients with uncontrolled T2DM in a cross-over fashion to either MDI or CSII. HbA1c decreased from  $9.0 \pm 1.6\%$  to  $8.6 \pm 1.6\%$  with MDI and  $7.7 \pm 0.8\%$  with CSII ( $P < 0.03$ ).<sup>7</sup> A study by Morera et al showed long-term efficacy of CSII in a cohort of 161 patients with T2DM over a period of 9 years. The mean HbA1c was  $9.0 \pm 1.7\%$  prior to start of CSII. After 1 year of pump therapy, mean HbA1c decreased by 1.3% compared to 0.8% with MDI ( $P < 0.001$ ). Over 9 years of follow-up, the HbA1c decrease was maintained ( $P < 0.05$ ), daily insulin requirements did not change, and weight gain was stable over 7 years.<sup>8</sup> In a study by Marchand et al, 157 patients were switched from MDI to CSII and showed reduction in HbA1c from  $8.4 \pm 1.3\%$  to  $7.7 \pm 1.3\%$  after 1-year CSII and remained lower than pre-CSII levels during 4 years of follow-up. Patients with pre-CSII HbA1c  $> 8.0\%$  showed significant improvement of HbA1c for 4 years, while those with pre-CSII HbA1c  $< 8.0\%$  showed no significant change.<sup>9</sup>

In clinical practice, particularly in adults, the HbA1c reduction can be several-fold greater than in these trials.<sup>3</sup> This reduction in HbA1c was without an increase in hypoglycemic episodes. Several meta-analyses have shown that CSII decreases the incidence of severe hypoglycemic events relative to MDI.<sup>10</sup> The most profound differences in these measures were seen in patients who have had diabetes for a long duration, with higher HbA1c levels, and higher baseline rates of severe hypoglycemia. As glycemic control directly affects cardiovascular morbidity and mortality, CSII has also shown favorable outcomes in coronary heart disease. In a large observational study comparing long-term effects of CSII versus MDI in 18,168 people with T1DM followed for 6.8 years, the adjusted hazard ratio for fatal coronary heart disease was 0.55 (95% CI 0.36-0.83).<sup>2</sup> Prior to 1993, it was suggested that patients using CSII had a higher incidence of DKA related to the lack of intermediate or long acting

insulin, lower total insulin doses and line blockages or pump failures. More recent data on modern CSII shows that there is no increased risk for DKA in CSII users, which may relate to less pump failures and better pump user education. In fact, there may be a decreased incidence of DKA-related hospitalizations in patients using CSII compared to MDI.<sup>11</sup> Overall, CSII therapy has received favorable reviews from patients, though we acknowledge that selection bias may contribute. According to a large meta-analysis, CSII therapy was related to improvement in depression, anxiety, responsibility for their regimen, self-esteem and family functioning. The most commonly perceived advantage was increased life-style flexibility.<sup>5</sup>

Fewer clinical investigations have examined CSII use in patients with T2DM. In a published analysis of several RCTs, no differences in the hypoglycemia risk with minimal to no significant HbA1c improvement were observed. Some trials showed a nonsignificant trend toward decreased insulin requirements in CSII patients with T2DM.<sup>4,7,10</sup>

While insulin pump therapy has the potential to benefit certain patients in real practice, several RCTs have shown no significant benefit of CSII over MDI regarding glycemic control. The REPOSE trial looked at MDI versus CSII after 1 week "skills training course" over a 2-year period. While both groups showed improvement overall in HbA1c and decreased hypoglycemic events, there were no significant differences between the groups. There was a modest improvement in quality of life in the CSII group. This suggests that the training and controlled environment contributed to the improved outcomes more than the mode of insulin delivery. Given the short acting analog used in CSII, reduced total daily insulin dose, and the ability to customize basal rates every hour, one would expect far less overnight hypoglycemic events in CSII versus MDI. The data on this is variable, especially in children.<sup>12</sup> While many observational studies do show a decrease in hypoglycemia in CSII, many randomized studies show no difference. Continuous glucose monitoring (CGM), particularly with alarms to alert to low or impending low glucose levels, would likely improve this outcome in both MDI and CSII groups.<sup>13</sup>

While CSII therapy has the potential to benefit patients in so many ways, it is important to keep in mind its limitations and downsides. Pump malfunction and failure rates are still relatively high, with as many as 50% of adult CSII users reporting a pump malfunction at some point. Infusion set/catheter related issues and occlusion can cause an interruption in insulin delivery, emotional distress and potential metabolic consequences, such as DKA. Patient education, the clinical team and insulin pump company help-lines can assist. Cutaneous complications including scarring, allergic reactions, lipohypertrophy and lipoatrophy are usually mild and do not cause patients to discontinue the pump. As with MDI infusion, set sites should be rotated and changed regularly, usually every 3 days. More severe cutaneous reactions like

**TABLE 1.** Clinical characteristics of suitable and unsuitable candidates for insulin pump therapy.

Clinical characteristics of patients who are not good candidates for insulin pump therapy	Clinical characteristics of patients who are suitable candidates for insulin pump therapy
<p>Unable or unwilling to perform MDI injections (<math>\geq 3</math>-4 daily), frequent self-monitored blood glucose (SMBG) (<math>\geq 4</math> daily), and carbohydrate counting.</p> <p>Lack of motivation to achieve tighter glucose control and/or a history of nonadherence to insulin injection protocols.</p> <p>History of serious psychological or psychiatric condition(s) (e.g., psychosis, severe anxiety, or depression).</p> <p>Substantial reservations about pump usage interfering with lifestyle (eg, contact sports or sexual activity).</p> <p>Unrealistic expectations of pump therapy (eg, belief that it eliminates the need to be responsible for diabetes management).</p>	<p>Patients with T1DM who do not reach glycemic goals despite adherence to maximum MDI, especially if they have:</p> <ul style="list-style-type: none"> <li>• Very labile diabetes (erratic and wide glycemic excursions, including recurrent DKA).</li> <li>• Frequent severe hypoglycemia and/or hypoglycemia unawareness.</li> <li>• Significant "dawn phenomenon," extreme insulin sensitivity.</li> </ul> <p>Special populations (e.g., preconception, pregnancy, children, adolescents, competitive athletes)</p> <p>Patients with T1DM who, after investigation and careful consideration, feel that CSII would be helpful in achieving and maintaining treatment targets and improve their ability to cope with the challenges of managing their diabetes.</p> <p>Selected patients with insulin-requiring T2DM who satisfy any or all of the following:</p> <ul style="list-style-type: none"> <li>• C-peptide positive, but with suboptimal control on a maximal program of basal/bolus injections (note: Centers of Medicare and Medicaid will not reimburse for pumps or pump supplies in T2DM patients who are not C-peptide deficient).</li> <li>• Substantial "dawn phenomenon."</li> <li>• Erratic lifestyle (e.g., frequent long-distance travel, shift work, unpredictable schedules leading to difficulty maintaining meal timing).</li> <li>• Severe insulin resistance, candidate for U-500 insulin by CSII.</li> </ul> <p>Selected patients with other DM types (e.g., postpancreatectomy).</p>

Adapted from 2014 AACE/ACE Consensus Statement.<sup>6</sup>

infections are rare, and can usually be prevented with proper education, skin preparation and frequent set changes.<sup>11</sup> Given these potential drawbacks and complications, it is important to start CSII therapy only on patients who are highly motivated and willing to be educated, including regarding carbohydrate counting and blood ketone testing, and to implement that education. Education of patients and their families about the insulin pumps' function, upgrades and malfunction, pump insertion site and a back-up plan are essential to success.<sup>10</sup>

Cost and insurance coverage are other factors to consider. Depending on the brand, the costs of an insulin pump and supplies could run between \$4,500 and \$6,500 for patients without insurance. In an economic analysis for patients with T1DM, pump therapy was not found to be cost-effective compared with MDI.<sup>14</sup>

## INDICATIONS AND CONTRAINDICATIONS FOR PRESCRIBING INSULIN PUMP THERAPY

CSII is not appropriate for every patient with insulin-requiring diabetes. [Table 1](#) reviews the proposed clinical characteristics of suitable and unsuitable pump candidates based on the American Association of Clinical Endocrinologists Insulin Task Force's comprehensive research and decades of clinical experience with CSII.<sup>10</sup>

It is also very important to take into consideration that prior to starting CSII therapy, patients should be referred to Certified Diabetes Educators to receive comprehensive diabetes education, including about carbohydrate counting, utilization of the insulin pump, while also managing hypoglycemia and hyperglycemia and sick-day care.

## MECHANISM OF INSULIN PUMP OPERATION

Insulin pumps are small programmable computerized devices which continuously deliver rapid-acting insulin over 24 hours, more closely mimicking physiologic insulin release. The pump offers the advantage of quantitative administration of a basal infusion of insulin. While a basal rate can be set hourly, basal rates lasting for 3-4 hours usually perform better due to insulin's action time of 3-4 hours. Pumps also enable personalized boluses with the meals, ideally based on food carbohydrate content, and for personalized correction boluses for high glucose corrections. Built-in calculators that suggest insulin doses for meals and corrections and also consider insulin remaining from any previous boluses and the patient's insulin action time give maximum dosing accuracy. The patient always has the option of overriding the suggested bolus dose.

### Basal Insulin

Basal insulin is the slow continuous insulin infusion required to maintain euglycemia and prevent ketosis. The initial basal rate is usually set to 50% of the total daily insulin requirement, which is usually 20-30% less than that when the patient was on MDI therapy, however, it may vary. One way of calculating total daily insulin requirement is by multiplying body weight in kg with 0.5 for adult patients.<sup>10</sup> Different basal rates can be programmed for variations in activities of daily living. A lower temporary basal rate can be introduced for a period of high activity such as exercise. Likewise, a higher temporary basal rate can be set for physical inactivity or during sick-days. The ratio of basal to bolus insulin is usually 50:50.

## Bolus Insulin

The bolus insulin is required to maintain euglycemia after food and is delivered before mealtime, or as a correction bolus to reduce above-target glucose levels. If the patient is above the prespecified target blood glucose level premeal, a correction dose is also included in the bolus. The bolus insulin dose is calculated based on the amount of carbohydrate ingested and insulin to carbohydrate ratio. The insulin to carbohydrate ratio is defined as the amount of carbohydrate (in grams) covered by each unit of (100 IU strength) insulin. The formula to calculate the initial insulin to carbohydrate ratio =  $450/\text{total daily insulin dose}$ .<sup>10</sup>

The insulin sensitivity factor (defined as the drop-in blood glucose level caused by each unit of insulin taken) is calculated initially by dividing 1,700 by the total daily insulin requirement. It is used with the bolus dose to correct for hyperglycemia. Usually the insulin to carbohydrate ratio and insulin sensitivity factor will be different at different times of the day, though one initially starts CSII therapy with a single insulin to carbohydrate ratio and insulin sensitivity factor (and a single basal rate).

Modern pumps also provide a feature of preset memory which calculates residual bolus insulin activity from the last insulin dose (i.e., an estimation of how much insulin is still active in the body) therefore reducing the risk of over-frequent corrections (insulin stacking) and hypoglycemia.

## INSULIN PUMP TYPES

Insulin pumps have evolved rapidly since their introduction nearly 40 years ago in order to become smaller,<sup>10,15,16</sup> more precise and more reliable.<sup>17</sup> The general trend is for the pumps to evolve toward an autonomous, integrated interstitial fluid glucose sensing and insulin delivery system, akin to an artificial pancreas.

Insulin pumps come in a variety of forms. A *patch insulin pump* is attached to the surface of the skin, with controls for the pump located on the device itself or on a remote control with integrated blood glucose meter. The insulin needle is part of the pump and it is inserted when the patch pump is attached. There is no tubing, and the pumps are safe for water immersion. Currently available patch pumps are V-GO and Omnipod.

*Tethered insulin pumps* are those that have a length of generic or proprietary flexible tubing between the pump itself and the cannula (the short, thin tube which goes through the skin). The pump itself, which usually feature controls, is free to be tucked into pockets or carried in pump pouches which can be worn under or outside of clothing. Commonly available examples of tethered pumps are Medtronic 630G, 670G and Tandem t: slim ×2.

An *implanted insulin pump* is a pump which remains at all times into the peritoneal cavity, which has a rich supply of blood vessels and can therefore absorb insulin very efficiently. These are rarely used, and users travel to

Montpellier, France several times a year to have their pumps refilled with insulin.

The functional aspects of insulin pumps vary widely, from the simple delivery system that requires total user control, to the recently available more complex, hybrid closed-loop systems that integrate an insulin pump with a CGM and use complex algorithms which allow partial autonomous functioning. The only clinically available hybrid closed-loop system is the Medtronic 670G, released in 2017 in the USA, which can help T1DM patients achieve time in glucose target range of 75–85% of the day. Users must still announce meals and estimate carbohydrate amounts and announce exercise.






The *V-GO patch pump* is a daily replaceable pump. It contains a preset amount of 20 units, 30 units or 40 units of U-100 rapid-acting insulin that is delivered constantly during the day as basal regimen, plus 36 units that can be optionally delivered by the user as boluses directly from the pump. It is a replacement for syringes and needles, approved only for D2M management.

The *Omnipod patch pump* can hold 200 units of U-100 rapid-acting insulin and lasts for up to 3 days. It is wirelessly controlled by a Personal Diabetes Management device with integrated glucometer, food library database and bolus calculator. The basal rate is user adjustable. A computer/smartphone app integrates the data from the pump, glucometer and CGM, to create reports and charts. The recent VIVID study showed benefits in using Omnipod with U-500 insulin for T2DM patients with high-insulin requirements (200–600 units a day).<sup>18</sup> The Pod is waterproof for up to 25 feet deep for 60 minutes, so there's no need to disconnect while swimming or bathing. A new DASH platform was FDA approved on June 4, 2018, which replaces the current Personal Diabetes Management controller with a locked-down Android phone. DASH loses the built-in glucometer, but it has a touch screen, Wi-Fi connectivity with software that can be remotely updated over the air and has other improvements.

The *Medtronic Minimed 630G* is a tethered pump that can hold 300 units of U-100 rapid-acting insulin. It has a bolus calculator and an optional glucometer that can send the data wirelessly to the pump. It can be integrated with a Medtronic Enlite CGM which measures interstitial fluid glucose levels to enable automated hypoglycemic episode mitigation through basal insulin delivery suspension at a preset low glucose limit. The pump is waterproof up to 12 feet deep for 24 hours.

The *Medtronic Minimed 670G* is a tethered pump that can hold 300 units of U-100 rapid-acting insulin and requires a Medtronic Guardian Sensor 3 CGM. If linked with a CGM, the system can act as a hybrid closed-loop system, allowing automated adjustments of daily basal insulin every 5 minutes based on CGM reading to a preset target blood glucose of 120 mg/dL, as well as hypoglycemic episode mitigation through predictive basal insulin delivery suspension at preset limits and automatic restart on recovery. It has a bolus calculator. It is protected against the effects of continuous immersion in up to 12

**TABLE 2.** Types of pumps and their main characteristics.

Pump type	Size (mm)	Weight	Connection	Type of insulin and total amount	Sensor integration	Software download	Water	Extra features
V-GO patch pump 	61 × 33 × 13	0.7-1.8 oz	Built-in	U-100 Humalog or Novolog 20, 30, or 40 units basal/24 h basal and bolus 2 units increments	None	V-Go software	Waterproof, 3 feet, 3 inches for 24 h	Provides glucose control without multiple daily injections. Releases a steady rate of rapid-acting <sup>1</sup> insulin for basal control. Delivers prandial insulin at the click of a button.
Omnipod patch pump 	Pod 61 × 41 × 18 Pda 66 × 110 × 26	OP: 1.2 oz (full reservoir) PDM: 4 oz (with battery)	Built-in	200 units of U-100 rapid acting insulin, U-500 insulin	None (independent use of Dexcom)	Not available	Only the Pod is waterproof for up to 25 feet deep for 60 min	Backlight, reminders and alerts, child lock, 1,000 foods in Pda, Tubeless, integrated with Freestyle meter.
Medronic Minimed 630G 	54 × 97 × 25	3.37 oz	Proprietary	300 units of U-100 rapid acting insulin	None	Not available	Waterproof, 12 feet for up to 24 h	Suspend basal on low. Does not have auto mode.
Medronic Minimed 670G 	54 × 97 × 25	3.37 oz	Proprietary	300 units of U-100 rapid acting insulin	Medronic	Not available	Waterproof, 12 feet for up to 24 h	Smart guard suspend before low, auto mode.
Tandem t: slim ×2 	79.5 × 50.8 × 15.2	3.95 oz with full reservoir	Proprietary, t: connect	300 units of U-100 rapid acting insulin	Dexcom G5 and G6	T: connect diabetes management application. Mac and PC compatible, Micro USB download of t: slim pump and supported meters	Watertight, 3 feet for 30 min	Only touchscreen insulin pump in the US, carb bolus allows grams for different food in a meal to be added individually, Insulin on Board displayed on home screen.

feet (3.6 meters) of water for up to 24 hours at a time. The Minimed 670G is indicated only for T1DM management for those aged 7 years or older.

The *Tandem t:slim* ×2 is a tethered pump that can hold 300 units U-100 of rapid-acting insulin. The pump software can be updated remotely from a computer. The device has a bolus calculator and it is watertight up to 3 feet of water for up to 30 minutes. The *t:slim* ×2 can be used independently, or together with a third-party CGM. The Dexcom 5 CGM integration allows trend monitoring on the pump screen and the setting of audible high and low glucose alerts. The new Dexcom 6 CGM allows, through a software update available in August 2018, predictive basal insulin delivery suspension at preset limits and automatic restart on recovery, like the Minimed 670 G, but not automated basal insulin adjustments. All Dexcom CGMs allow glucose data to be shared in real time on Apple/Android smartphones and the Apple Watch with up to 5 caregivers, with the option of setting customizable glucose alerts for followers.

Table 2 includes the pump models and their relevant features.

## CONCLUSIONS

Insulin pump therapy has made tremendous progress in the last 4 decades to become an increasingly common tool in the modern management of patients with diabetes. As technology advances, patients requiring insulin and their healthcare providers must work together to take full advantage of potential benefits and rise to prospective challenges.

## AUTHOR CONTRIBUTIONS

N.D.S. and A.J.J. contributed to the design of the manuscript, the main conceptual ideas. N.D.S. analyzed the data and proof outline. N.D.S., A.J.J., F.S., E.A.B. acquisitioned, analyzed, and interpreted the data, created the draft, and did the critical revision.

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