Continuous Subcutaneous Insulin Delivery Systems

Subjects: Medicine, Research & Experimental

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An insulin pump is an electronic device that releases rapid insulin according to the body's daily needs. Insulin pumps deliver insulin in two primary ways: A continuous infusion of small amounts of rapid insulin throughout the day and night (basal rate) and A one-time dose of rapid-acting insulin for meals or high blood glucose correction (bolus).

type 1 diabetes mellitus | insulin | diabetes management | technology | continuous glucose monitoring systems | insulin pumps

1. Introduction

The ideal individuals for insulin pump use are:

- People with Type 1 Diabetes (T1DM) or insulin-dependent Type 2 diabetes (T2DM);
- People with multiple-day injections of insulin;
- People who can assess appropriate blood glucose control;
- Capable of performing insulin pump therapy initiation and maintenance;
- Able to maintain frequent contact with the healthcare team;
- Able to consider insulin pumps as a tool to improve diabetes care;
- Capable of accurately calculating carbohydrates and insulin bolus;
- Individuals with critical clinical conditions who have serious difficulties controlling glycemic targets, despite intensive treatment and monitoring;
- With substantially decompensated diabetes (frequent severe hypoglycemia and/or hyperglycemia);

- Other associated conditions: extreme insulin sensitivity, gastroparesis, pregnancy, variable schedules or work shifts, significant “dawn phenomenon”, high insulin dose therapy, or severe insulin resistance.

2. Conventional Insulin Pumps

An insulin pump is a small digital device that ensures a continuous infusion of rapid-acting insulin (CSII). The infusion set is inserted into the subcutaneous tissue and fixed on the skin with an adhesive. In most insulin pumps, the infusion set connects to the pump by plastic tubing. Insulin infuses from the pump through the tubing to the infusion set cannula and into the subcutaneous tissue. The most common devices are displayed in **Table 1**.

Table 1. Comparison between various commercially available CSII pumps.

	AccuChek Spirit Combo	Medtronic Paradigm 522/722	Medtronic 720G	Omipod Patch Pump	Cellnovo Insulin Pump	Dana Diabecare R
Producer	Roche Pharma	Medtronic	Medtronic	Insulet Corporation	Cellnovo	Sooil
Weight (g)	80	100	105		30	51
Dimensions (mm)	80 × 56 × 20	51 × 79 × 20	96 × 53 × 25	Pod: 41 × 61 × 18 PDA: 66 × 110 × 26	NA	54 × 75 × 19
Insulin Volume per Infusion Set (mL)	315	176-300	300	200	150	300
Basal Increments (units)	0.1	0.05	0.025	0.05	0.05	0.1
Basal Delivery minim (units)	3	10	3	3	3	3
Bolus Increments minim (units)	0.1, 0.2, 0.5, 1,2	0.1	0.025	0.05	0.05	0.1–87
Basal Rates/24 h (units)	24	48	48	48	24	48
Basal Profiles (units)	5	3	8	7	20	4
Bolus Calculator	On separate device	Yes	Yes	Yes	Yes	Yes

	AccuChek Spirit Combo	Medtronic Paradigm 522/722	Medtronic 720G	Omipod Patch Pump	Cellnovo Insulin Pump	Dana Diabecare R
Multiple Bolus-type Options	Yes	Yes	Yes	Yes	Yes	Yes

NA = not available.

n delivery
intended
for insulin therapy aim to be small and disposable, and easy to handle and carry. There are three categories of PPs: PPs with reduced features, fully equipped PPs, and PPs suitable for automatic insulin delivery (AID) systems.

The reduced-features PP delivers only basal insulin. A fully equipped PP delivers a variable amount of basal insulin over 24 h and has a bolus button that permits prandial insulin to be given in two-unit increments daily.

Full-featured electromechanical patch pumps generally have an electromechanical structure with an electronic controller. These are all full-featured pumps with different basal rates, individually controllable bolus amounts, and additional means of bolus delivery.

PPs are small, easy to use, and discreet to wear. Moreover, they can interact with the CGM and AID systems' algorithms.

3. Sensor-Augmented Pump (SAP)

An SAP is a CSII that can integrate data from a CGM system. Glycemia is displayed on the pump in real time. It is used by the pump algorithm to automatically stop the basal insulin infusion (for up to 2 h) as a response to detected/predicted hypoglycemia. Then, the basal insulin infusion is released at the previously programmed rate. This feature helps diminish moderate-to-severe hypoglycemia, especially during nighttime, and reach better glycemic control [1]. SAPs are known as open-loop systems [2].

There are two types of SAPT available on the market:

- Low-glucose suspend (SAPT-LGS): Suspends basal rate when hypoglycemia occurs.
- Predictive low-glucose management (SAPT-PLGM): Can suspend basal rate before hypoglycemia occurs.

SAP can reduce hypoglycemia by 40–50% (<70 mg/dL) without an increase in glycosylated hemoglobin [3][4][5][6].

4. Closed-Loop Insulin Systems (Artificial Pancreas)

A CGM could become a part of a CSII through an algorithm, generating a closed-loop insulin system. It is a substantially improved system, adjusting insulin delivery in response to real-time sensor glucose levels and other inputs, such as meal intake. Control algorithms can modulate the insulin needs' variability between and within individual users, considering CGM accuracy limitations and insulin delivery imprecision [7].

The three main components of a closed-loop system are:

- Glucose measuring device (CGM);
- Control device for BG analysis and insulin dosing regulation (computer/microprocessor);
- Insulin infusion device (insulin pump).

The control algorithms are continuously adapted to physiological changes with real-time adjustment of closed-loop control parameters.

Various control algorithms were developed [8]: model predictive iterative learning control (MPC) [9][10][11], proportional integral derivative (PID) controllers [12][13], and fuzzy logic control approaches [14][15].

The closed-loop system functions as a pancreas that controls BG levels. Thus, the closed-loop insulin system is known as the artificial pancreas (AP) [16]. When an AP system requires counting and registering the carbohydrate amount from mealtime, it is called a "hybrid" [17] because a part of insulin is provided automatically, and another is infused based on the reported information.

In 2016, the FDA approved the first hybrid closed-loop system [18]. It automatically gives a suitable amount of short-acting insulin at a basal rate. The patient still needs a glucose meter a few times daily, manually adjusting the insulin delivery at mealtimes and when it requires a dose correction. Nowadays, there are several FDA- and EMA-approved systems: Medtronic 770/780G, Tandem Control IQ, Omnipod 5, CamAPS, Diabeloop, etc. (**Table 2**).

Table 2. Comparison between various commercially available hybrid closed-loop systems [19].

	Tandem t:Slim X2 Control IQ	Medtronic 780G	Omnipod 5	CamAPS FX
Producer	Tandem Diabetes Care, San Diego, CA, USA	Medtronic plc, Dublin, Ireland	Insulet Corporation, Acton, MA, USA	CamDiab Ltd., London, UK
Pump	Tandem	Medtronic	Omnipod	Dana, Ypsopump
CGM	Dexcom G6	Guardian 3 and 4	Dexcom G6	Dexcom G6, Freestyle Libre 3
CGM duration (days)	10	7	10	10/14
Algorithm type	MPC	PID	MPC	MPC
Algorithm configuration	On pump	On pump	On pump	App on Android smartphone
Approved for ages (years)	6 and above	7 and above	2 and above	1 and above

	Tandem t:Slim X2 Control IQ	Medtronic 780G	Omnipod 5	CamAPS FX
Weight (g)	112	105	Pod 26 PDA 165	NA
Dimensions (mm)	79 × 51 × 15	96 × 53 × 25	Pod 39 × 52 × 14.5	NA
Tubeless	No	No	Yes	No
Insulin volume per infusion set (mL)	300	300	85–200	300
Minimum basal increments (units)	0.001	0.025	0.05	NA
Bolus range (units)	0–25	0–25	0.05–30	
Minimum daily dose (units)	10	8	6	5
Algorithm target (mg/dL)	110–160	100 or 120	110–150	104 (80–198)
Meal detection	No	Yes	No	No

[20][21][22] the next- ... agement. ... ple [23]. In May 2023, the Beta Bionics Inc. (Boston, MA, USA) iLet ACE Pump and iLet Dosing Decision Software pancreas system [20][22][24][25][26] received FDA approval.

Data are available in each product's technical specifications, adapted from https://www.pcdsociety.org/resources/details/diabetes-technology-state-art, accessed on 10 March 2023. NA = not available.

Like a healthy pancreas, an utterly automated closed-loop system does not request meal announcements; it can react to BG level variations [27]. The benefits and limitations of closed-loop systems are given in **Table 3**.

Table 3. Benefits and limitations of closed-loop systems.

Closed-Loop Insulin Systems Benefits	Closed-Loop Insulin Systems Limitations
The glucose levels can be continuously monitored.	The T1DM patient regularly verifies the devices to ensure that they function correctly.
The control algorithms improve BG control, automatically regulating the amount of insulin.	The user must continuously verify the CGM and infusion pump catheter, ensuring they are in a suitable place, and change them when needed.
The system helps the T1DM user avoid emerging events (hypoglycemia and hyperglycemia).	The CGM accuracy should be verified, and the CGM sensor must be regularly replaced.
	The patient must count the mealtime carbohydrates and enter them into the system.
	The control software settings must be verified to ensure that the insulin infusion has a suitable amount.

Closed-Loop Insulin Systems Benefits	Closed-Loop Insulin Systems Limitations
	The extreme BG levels should be regulated if the system is unable.
	The pump’s algorithm could not predict exercise.

- Hypoglycemia occurs when a significant basal rate of insulin is delivered due to a human error in insulin pump programming or a device malfunction.

- Hyperglycemia is caused by programming error or device malfunction, leading to a low insulin delivery rate (battery depletion or malposition, cannula occlusion, total pump failure).

- If the infusion set is not changed regularly, at 3–4 days, there are irritation and infections at the place of cannula insertion.

- Insulin pump therapy discontinuation (18–50%) is the T1DM patient choice for various reasons: unwanted interference with the lifestyle, missing improvements in glycemic control, and infection at the insertion place. It occurs with high incidence in women, younger individuals, pregnancy, and when the patient has psychological comorbidities.

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