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A Hybrid Closed-Loop Insulin Delivery System for the Treatment of Type 1 Diabetes

Image courtesy of Medtronic

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Summary

- Because their bodies no longer produce enough insulin, people with type 1 diabetes mellitus must check their blood glucose — or blood sugar — levels several times a day and then calculate and inject an appropriate insulin dosage.

- Wearable systems, sometimes referred to as an "artificial pancreas," are now available to replicate some of the functions of the pancreas in controlling insulin delivery.

- The MiniMed 670G is currently the only hybrid closed-loop system licensed for commercial use.

- Available evidence supports the safety of the MiniMed 670G system for individuals with type 1 diabetes who are 14 years of age and older. Several further studies are underway, including a study in children and a larger randomized controlled trial.

- The manufacturer, Medtronic, expects the MiniMed 670G will be available in the US in the spring of 2017. Its availability in Canada is not yet known.

Issue

In people with type 1 diabetes, the pancreas either does not produce any insulin, or it does not produce enough insulin. People with type 1 diabetes need to take insulin daily to maintain blood glucose — or blood sugar — levels within the target range.[1] They must frequently check glucose levels using a finger-stick test or a continuous glucose monitor and then determine the correct insulin dose to administer. Taking too much insulin can lead to hypoglycemia, or low blood sugar — a particular risk when this occurs overnight. Taking too little insulin can lead to hyperglycemia, or high blood sugar, and diabetic ketoacidosis — a build-up of chemicals called ketones that are produced when the body uses fat instead of sugar to make energy.[1,2] These conditions, as well as high and low swings in blood glucose levels, are associated with increased morbidity and mortality.[1]

Wearable systems are available for the continuous management of type 1 diabetes. These systems are intended to control blood glucose during particularly challenging times, such as overnight, at meal times, and when exercising.[3]

Automating the delivery of insulin in wearable systems combines three functions:

- continuous glucose monitoring
- insulin delivery via a pump
- control of insulin using specific algorithms (a set of rules used by a computer program to make calculations).[4]

The continuous glucose monitor sends glucose values to the insulin pump, and an algorithm determines the amount of insulin needed based on the sensor values and the amount of active insulin in the individual.[4,5] Integrating these three functions creates a closed-loop system, without any intervention from the user — in other words, an artificial pancreas.[4,5]

In contrast, a hybrid closed-loop system still needs user interventions (for example, fast-acting bolus insulin doses taken at meal times).[4]

One hybrid closed-loop insulin delivery system, the MiniMed 670G (Medtronic, Dublin, Ireland), is now available in the US.

The Technology

The MiniMed 670G is a hybrid, closed-loop, insulin delivery system made up of various components that perform different functions:[6]

- The Guardian Sensor, which is inserted under the skin using a small insertion device and taped in place for a single-use, seven-day period. It measures glucose levels in the fluid surrounding the cells below the skin (interstitial fluid). The sensor does not replace finger-stick tests for determining insulin requirements for meals and activities. It also requires a minimum of two finger-stick calibrations against the system's glucose metre every day; four calibrations are recommended.

- The CONTOUR NEXT LINK 2.4 glucose metre, with test strips, for finger-prick capillary blood sampling to calibrate the system. Glucose values are automatically transmitted to the insulin pump.
- The MiniMed 670G insulin pump — a waterproof, battery-operated, rate-programmable, micro-infusion pump that delivers insulin from a reservoir.
- The Guardian Link Transmitter, in conjunction with the glucose sensor, which collects and wirelessly transmits interstitial glucose values to the insulin pump. The MiniMed 670G system can store up to 90 days of pump and glucose sensor data.

The system can be used in either automatic or manual mode, but in both modes the user must manually enter the estimated carbohydrates to be consumed at meals and accept mealtime insulin boluses suggested by the system.[4-8] In automatic mode, the system uses an algorithm to automatically adjust basal insulin (insulin that keeps your blood sugar stable between meals or during sleep) delivery in response to fluctuations in interstitial glucose levels. In manual mode, the user can set the pump to suspend activity at or before low glucose values. Insulin delivery will automatically suspend activity when the glucose level drops or is predicted to drop to a selected threshold (e.g., low blood glucose in the 2.8 mmol/L to 5.0 mmol/L range).[6] Remote transmission of data from the system and monitoring via telemedicine is possible.[6,9]

Availability

The MiniMed 670G system is not yet licensed by Health Canada.

In the US, the MiniMed 670G system received FDA approval in September 2016.[6] The system received a priority review because it is a novel technology and availability was considered to be in the best interests of patients.[6] The FDA approval states that the system is intended for continuous delivery of basal insulin at user selectable rates, and administration of insulin boluses in user selectable amounts, for the management of type 1 diabetes in persons aged 14 and older.[6] Medtronic plans to market the system in the US in the spring of 2017, and outside the US later in 2017.[10]

Cost

In Canada, although the purchase costs of the system are not yet known, Medtronic estimates that the annual operating costs will be in the C$8,500 to C$9,500 range, excluding the cost of insulin, and will be comparable to the operating costs of existing insulin pump technologies with continuous glucose monitoring. (Ruth Pichora, Medtronic, Diabetes Canada, Brampton, ON: personal communication, 2017 Mar 7).

Who Might Benefit?

Currently, the MiniMed 670G is intended for use by people older than 14 who have type 1 diabetes and require at least eight units of insulin daily.[6] At this time, it is not intended for use by children under the age of seven because they usually require less than this amount of insulin.[6] However, there are efforts underway in the US to expand the age range to children younger than 14 years of age (Ruth Pichora: personal communication, 2017 Mar 7). People with significant nocturnal hypoglycemia, or hypoglycemia unawareness, could particularly benefit from this type of technology.[1,11] Because the system requires finger-stick tests for calibration, and before meals and activities, it is not suitable for patients unwilling or unable to do frequent finger-stick glucose measurements.[6]

Current Practice

The Diabetes Control and Complications Trial (1983 to 1993) revolutionized the treatment of type 1 diabetes by showing that intensive glycemic control, beginning as soon as possible after diagnosis, prevents or delays diabetes-related complications of the eyes, kidneys, and nerves.[12] A large, more recent study found that higher average blood glucose levels and increased proteinuria, which is abnormally high levels of protein in the urine, were major risk factors for death, demonstrating how important glycemic control is for contributing to longer and healthier lives for people with type 1 diabetes.[12]

The current approach to managing diabetes is for a multidisciplinary team, using a patient-centred approach, to set glycemic targets according to individual circumstances (e.g., diet, age, weight, hypoglycemia awareness status, ability for self-management, patient preferences), and to offer structured educational programs to promote patient empowerment.[2,13] Insulin is administered either by multiple daily injections or by

an insulin pump that delivers a continuous subcutaneous insulin infusion.[2] Long-acting and ultra-long-acting insulins can be combined with rapid-acting insulins to provide effective basal bolus therapy to reflect physiological insulin secretion.[13]

The Evidence

Currently, the evidence for the effectiveness of the MiniMed 670G device consists of one small randomized controlled trial, reported in a conference abstract[14] and a prospective before-and-after cohort study submitted to the FDA (Table 1).[6,15,16]

The randomized controlled trial described the safety and efficacy of a preliminary algorithm for the MiniMed 670G in 21 teens and young adults with type 1 diabetes at a diabetes camp.[14] Patients were randomized to receive the MiniMed 670G or the MiniMed 530G (an earlier Medtronic system), with a suspension threshold of 3.3 mmol/L, over six days and nights.

The prospective before-and-after study, funded by Medtronic, focused on safety.[6,15-18] Although some efficacy results were provided, the study was not designed to show efficacy.[6] The study was carried out at 10 centres (nine in the US and one in Israel) from June 2015 to March 2016. The study enrolled 126 patients with type 1 diabetes; 123 completed the study. A two-week baseline run-in period was followed by a three-month study period. Safety end points were: incidence of severe hypoglycemia and diabetic ketoacidosis, serious adverse events, and device-related serious or unanticipated adverse events. Efficacy end points included time in open- versus closed-loop systems; percentage of sensor glucose values below, within, and above the target range (3.9 mmol/L to 10.0 mmol/L); changes in glycated hemoglobin (A1C), insulin requirements, and body weight; and measures of glycemic variability.

Clinical Efficacy and Effectiveness

Results of the randomized controlled trial showed that both the MiniMed 670G system and the MiniMed 530G system worked well during the day, with similar glucose values within the target range of 3.8 mmol/L to 10.0 mmol/L. However, the MiniMed 670G was associated with less hypoglycemia overnight — experienced by 1.3% of patients with the MiniMed 670G versus 5.2% with the control device.[14]

Efficacy data from the prospective before-and-after study (Table 1) included a drop in mean A1C levels and an increase in the percentage of time that blood glucose was in the target range; no statistics were provided.[6,15-18]

Safety

According to the FDA safety summary, two potential device-related serious adverse events are: diabetic ketoacidosis from high blood glucose due to inadequate or suspended insulin delivery, and severe hypoglycemia from over-delivery of insulin.[6] Potential device-related, non-serious events include: skin irritation or redness, infection, pain or discomfort, bruising, swelling, rash, bleeding, induration (hardening) of the skin, and allergic reactions to the skin adhesives.

The prospective before-and-after study reported few serious or device-related adverse events.[6,15] During 12,389 patient-days, there were no device-related serious adverse events (episodes of severe hypoglycemia or diabetic ketoacidosis). However, there were 28 device-related adverse events that were resolved at home. These included 17 episodes of severe hyperglycemia (glucose greater than 16.6 mmol/L, with blood ketones greater than 0.6 mmol/L or accompanied by symptoms of nausea, vomiting, or abdominal pain), six episodes of less severe hyperglycemia, four reports of skin irritation, and one report of rash. No adverse events were reported in the small randomized controlled trial.[14]

Cost-Effectiveness

A recent cost-effectiveness analysis performed from a UK National Health Service perspective, used technologies that combined sensor-augmented insulin pump therapy with continuous glucose monitoring (referred to as "the newer paradigm") compared with insulin pump therapy with patient self-monitoring.[19] Results showed the newer paradigm was associated with higher average quality-adjusted life expectancy (18 quality-adjusted life-years versus 15 quality-adjusted life-years), and higher life expectancy (24 years versus 22 years). But there were also higher average lifetime direct costs equivalent to C$206,000 versus C$145,000, leading to an incremental cost-effectiveness ratio equivalent to C$20,000 per quality-adjusted life-year gained (all figures rounded).

Upcoming Research

At least four studies of the MiniMed 670G are underway or planned (see Table 2). Two are of particular interest, both of which are funded by the manufacturer:

- The Safety Evaluation of the Hybrid Closed Loop (HCL) System in Pediatric Subjects With Type 1 Diabetes is investigating the safety of the MiniMed 670G in children two to 13 years old.[20]
- The Multi-center Trial in Adult and Pediatric Patients With Type 1 Diabetes Using Hybrid Closed Loop System at Home (NCT02748018) is planned as a randomized, parallel group study, with recruitment of 1,500 people with type 1 diabetes. The trial will test three MiniMed 670G settings against control groups, using multiple-dose injections, insulin pump technology alone, and sensor-augmented pump technology.[21]

Concurrent Developments

A recent UK horizon scanning report on artificial pancreas devices identified 18 closed-loop systems in various stages of development.[4] All were in clinical trials prior to potential commercialization, although only five of the devices were expected to be marketed in the European Union by 2018.[4] Of particular interest is a technology from Boston — the Physiologic Insulin Delivery with Adaptive Basal (PIDAB) — that eliminates the need for pre-meal carbohydrate calculations, as it includes a meal identification algorithm to deliver insulin in several boluses: within the first 15 to 30 minutes of a meal, at 30 to 45 minutes, and at 60 minutes.[4]

> "Surveys of potential users of closed-loop insulin delivery systems have found considerable interest in using these technologies."

Glucagon has also been a focus of recent diabetes research. Glucagon is a hormone produced by the pancreas to correct hypoglycemia. One approach to the management of type 1 diabetes is a dual-hormone system that automatically delivers both insulin and glucagon.[3,22] In dual-hormone systems, the addition of glucagon could be used to reduce hypoglycemia or mean glucose concentrations in one of two ways: by adding glucagon to reduce hypoglycemia without increasing the level of insulin delivery, or by delivering insulin more aggressively and counteracting it with glucagon when necessary.[22] However, the use of glucagon is limited by problems that arise following reconstitution, as it forms amyloid fibrils, or fibres, that can clog or obstruct pump hardware.[3]

With respect to curative therapy for type 1 diabetes, research on pancreas or islet cell transplantation is underway but has been limited by organ availability and the risks associated with immunosuppression. The quest for a bioartificial pancreas is also ongoing, as this would alleviate the need for immunosuppression.[3,23] In a bioartificial pancreas, pancreatic islets (porcine, human, or derived from embryonic stem cells) are enclosed in a biocompatible agent to allow nutrient, insulin, and glucose exchange; human trials with this method are underway.[3,23] (Another bulletin in this series looks at the evidence to date on ViaCyte's islet cell replacement therapy (ViaCyte, San Diego, California.)

Implementation Issues

Uptake

Surveys of potential users of closed-loop insulin delivery systems have found considerable interest in using these technologies. For example:

- In a survey of people with type 1 diabetes in England, 240 of 266 respondents (90%) said they were extremely or highly likely to use a fully-automated, 24-hour artificial pancreas if it was available.[24] The researchers noted that, despite perceived potential disadvantages, there was a strong need for a device that will minimize the burden of disease, facilitate improved psychosocial functioning, and improve quality of life.
- Similarly, in a French study that presented information on the artificial pancreas to 101 people with type 1 diabetes, most patients expressed a desire to have such a system, and the proportion noting it was extremely likely they would replace their current insulin pump with an artificial pancreas system rose from 24% to 41% after the information session.[25] Two factors were associated with an interest in using an artificial pancreas: recent disease onset, and current use of an insulin pump rather than multiple daily injections.

- In Italy, a study of the attitudes of 27 parents of children with type 1 diabetes found that most parents were supportive of the artificial pancreas model.[26] The perceived advantages of the model were stable glucose regulation, relief of daily concerns, and reduced need for nocturnal monitoring, with patients being confident about the positive impact on disease control and their ability to use the system. Perceived disadvantages were the need to constantly deal with a bulky device and the risk of technical error. All parents stated their intention to use the technology when it became available.
- Regarding physician attitudes, a survey of 105 European endocrinologists indicated positive intentions toward prescribing the artificial pancreas (mean score of 5.5 on a 7-point Likert scale).[25]

Despite the interest of parents, patients, and physicians, experts have noted that earlier advances, such as continuous glucose monitoring, have not yet become standard reimbursed diabetes therapies for a number of reasons:

- Rapid changes, such as exercise and meals, make continuous glucose monitoring less accurate than capillary finger-stick samples because of the lag time between capillary and interstitial readings.
- Sensors require frequent replacement.
- Sensors must be inserted into the skin.
- Sensor accuracy is not always optimal, particularly in the hypoglycemic range.
- Recalibrations with finger-prick samples are still required.
- An annual cost of continuous glucose monitoring in the US is US$3,000 to US$4,300.[27,28] Medtronic estimates the cost of continuous glucose monitoring, based on the use of 60 sensors per year, is approximately C$3,600 (Ruth Pichora: personal communication, 2017 Mar 7).

Final Remarks

Authors of the recent UK briefing on artificial pancreas technologies noted that widespread adoption will depend on evidence that these systems are safe and effective in real-life settings over longer periods of time, and that they are cost-effective and acceptable to users.[4]

The cost of the devices and their annual operating costs may be a financial burden for people with diabetes and their families. Decisions about the public funding of these technologies will become important.

Methods — Literature Search Strategy

A limited literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and the Cochrane Library. Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (cadth.ca/grey-matters). No methodological filters were applied. The search was limited to English-language documents published between January 1, 2015, and January 19, 2017. Conference abstracts were included in the search results. Regular alerts updated the search until project completion; only citations retrieved before March 6, 2017 were incorporated into the analysis.

Table 1: Characteristics and Findings of Included Studies

First Author (Year), Site, Country, Funder	Study Design and Study Exclusions	Patient Characteristics	Intervention and Comparator	Study Duration and Clinical Outcomes Tracked	Findings
Ly et al. (2015), Stanford University, CA, US14 Conference abstract Funder NR (6 of 10 authors were employed by Medtronic)	Prospective RCT at a DM camp Study exclusions: NR	n = 20 patients with T1DM; sex distribution NR, mean age 18.6 years (SD 3.7), mean DM duration 9.1 years (SD 4.7), mean total daily insulin 0.8 U/kg (SD 0.2), mean A1C 8.6% (SD 1.5%)	MiniMed 670G (intervention) or 530G with threshold suspend at 3.3 mmol/L (control)	Duration: 6 days and nights at DM camp Outcomes: % of time in closed (vs. open) loop mode, % of time glucose was in target range (3.9 to 10.0 mmol/L) daytime (7 a.m. to 11 p.m.) and overnight (11 p.m. to 7 a.m.)	Safety: NR Efficacy: • Patients in the 670G group remained in closed loop 93% of the time. • Glucose in the target range, daytime, was similar between groups; 68.5% vs. 69.3%, control vs. 670G, respectively, P = 0.89. • Glucose in the target range, overnight, had less nocturnal hypoglycemia; < 3.9 mmol/L in the 670G group, P = 0.003.
Bergenstal et al. (2016), International Diabetes Center, Minneapolis, MN, US6,15-18 NCT02463097 Funder: Medtronic	Prospective observational before-and-after safety study at 10 centres (9 in US, 1 in Israel), June 2015 to March 2016. Many study exclusions including 2 or more episodes of severe hypoglycemia or DKA in previous 6 months	n = 126 patients with T1DM (of which 3 did not complete); 56% women, mean age 37.8 years (SD 16.5, range 14 to 75), mean DM duration 21.7 years, mean total daily insulin 47.5 U (SD 22.7 U), mean A1C 7.4% (SD 0.9%)	MiniMed 670G (no comparator)	Duration: 2-week run-in, then 12-week study period including a 6-day hotel stay: 12,389 patient-days Outcomes: (a) Safety: severe hypoglycemia, DKA, SAEs, device-related SAEs and AEs (b) Effectiveness: % of time in closed- (vs. open-) loop mode, A1C levels, daily insulin dose, glycemic variability	Safety: • No episodes of severe hypoglycemia or DKA • No device-related SAEs. 4 SAEs not related to the system (appendicitis, bacterial arthritis, worsening rheumatoid arthritis, Clostridium difficile diarrhea) • 28 device-related AEs that resolved at home, including 17 episodes of severe hyperglycemia (glucose > 16.0 mmol/L) due to the infusion set, software or hardware issues, or sensor issues • 117 AEs not related to the system including 7 episodes of severe hyperglycemia due to intercurrent illness or other non-system causes Efficacy: • % of time in closed-loop mode: median 87.2% • A1C levels: dropped from a mean of 7.4% to 6.9% • Daily insulin dose: increased from 47.5 U to 50.9 U • % of glucose in target range: increased from 66.7% to 72.2%

A1C = glycated hemoglobin; AE = adverse event; CA = California; DKA = diabetic ketoacidosis; DM = diabetes mellitus; MN = Minnesota; NR = not reported; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation; T1DM = type 1 diabetes mellitus; U = unit; vs. = versus.

Table 2: Studies Under Way or Pending for MiniMed 670G

Study Identifier, Country, Dates, Sponsor	Study Status and Phase	Study Design and Main Study Exclusions	Patient Group	Intervention	Follow-up and Clinical Outcomes Tracked
NCT02660827[20] International — 10 centres (9 in US, 1 in Israel) April 2016 to April 2018 Medtronic	Recruiting Phase IV	Prospective cohort safety study at home in children with T1DM on insulin pump therapy, aged 2 to 13 Exclusions: > 2 episodes of severe hypoglycemia or DKA in past 6 months	n = goal of 120 children with T1DM	670G system (primarily testing the algorithm)	Follow-up = 3 months after a 2-week run-in period Safety: Event rates of severe hypoglycemia and DKA Efficacy: Change in A1C
NCT03017482[29] US (Stanford University) February 2017 to February 2019 Stanford University	Not yet open for recruitment	Prospective cohort study in patients starting on 670G (aged 7 to 13; i.e., not currently approved for use by the FDA) Exclusions: Pregnant or planning pregnancy in next 12 months	n = goal of 100 people aged 7+ with T1DM who are planning to start using the 670G	670G system	Follow-up = 12 months Safety: Event rates of severe hypoglycemia and DKA by 12 months Efficacy: % of time patients use closed-loop by 6 months (goal > 70%); % of time in range (3.9 mmol/L to 10.0 mmol/L)
NCT03040414[30] International — 10 centres (4 in US and 1 each in Germany, Israel, Slovenia) December 2017 to June 2020 HealthPartners Institute, NIDDK, Medtronic	Not yet open for recruitment	Prospective randomized, open-label crossover study comparing two automated insulin delivery system algorithms (670G vs. next-generation 690 that uses fuzzy logic) Exclusions: 1+ episode of DKA in past 6 months and multiple others	n = goal of 112 teens and young adults, aged 14 to < 30 years, with T1DM	670G versus next-generation 690 that uses a fuzzy logic algorithm — 12 weeks, 4 week washout, 12 weeks alternative system	Follow-up = 5 months Safety: Event rates of severe hypoglycemia and DKA Efficacy: % of time blood glucose is > 10.0 mmol/L from 7 a.m. to 11 p.m., in target range (3.9 mmol/L to 10.0 mmol/L), and < 3.9 mmol/L QoL and DM technology attitudes questionnaires
NCT02748018[21] International — up to 70 centres in the US, Canada, Europe, and elsewhere January 2017 to August 2020 Medtronic	Not yet open for recruitment Phase III	Prospective, multi-centre, randomized, parallel adaptive study in T1DM in the home setting Exclusions: multiple	n = goal of 1,500 people, aged 7 to 75 years, with T1DM	4 study groups: MDI 670G 670G without the glucose sensor 670G without low management suspend	Follow-up = 6 months Safety: Event rates of severe hypoglycemia and DKA Efficacy: % of time blood glucose is in the target range (3.9 mmol/L to 10.0 mmol/L), and < 3.9 mmol/L; change in A1C

A1C = glycated hemoglobin; DKA = diabetic ketoacidosis; DM = diabetes mellitus; MDI = multiple daily injections; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; QoL = quality of life; T1DM = type 1 diabetes mellitus; vs. = versus.

References

1. Hanazaki K, Munekage M, Kitagawa H, Yatabe T, Munekage E, Shiga M, et al. Current topics in glycemic control by wearable artificial pancreas or bedside artificial pancreas with closed-loop system. J Artif Organs. 2016 Sep;19(3):209-18.

2. Pharmacotherapy in type 1 diabetes: executive summary. Can J Diabetes [Internet]. 2013 [cited 2017 Feb 15];37:S310-S311. Available from: http://www.canadianjournalofdiabetes.com/article/S1499-2671(13)00061-0/pdf

3. Malek R, Davis SN. Novel Methods of Insulin Replacement: The Artificial Pancreas and Encapsulated Islets. Rev Recent Clin Trials. 2016;11(2):106-23.

4. Trevitt S, Simpson S, Wood A. Artificial Pancreas Device Systems for the Closed-Loop Control of Type 1 Diabetes: What Systems Are in Development? J Diabetes Sci Technol [Internet]. 2016 May [cited 2017 Jan 31];10(3):714-23. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5038530/pdf/10.1177_1932296815617968.pdf

5. Minimed 670G: A hybrid closed-loop insulin delivery system. Med Lett Drugs Ther. 2016;58(1508):147-8.

6. MiniMed 670G system. In: Summary of safety and effectiveness data (SSED) [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2016 [cited 2017 Feb 15]. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017B.pdf

7. Ly TT, Weinzimer SA, Maahs DM, Sherr JL, Roy A, Grosman B, et al. Automated hybrid closed-loop control with a proportional-integral-derivative based system in adolescents and adults with type 1 diabetes: individualizing settings for optimal performance. Pediatr Diabetes. 2016 May 18. Epub ahead of print.

8. Kropff J, Devries JH. Continuous Glucose Monitoring, Future Products, and Update on Worldwide Artificial Pancreas Projects. Diabetes Technol Ther [Internet]. 2016 Feb [cited 2017 Jan 31];18 Suppl 2:S253-S263. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4717501/pdf/dia.2015.0345.pdf

9. Oron T, Farfel A, Muller I, Miller S, Atlas E, Nimri R, et al. A remote monitoring system for artificial pancreas support is safe, reliable, and user-friendly. Diabetes Technol Ther. 2016;18 Suppl 1:S93-S94.

10. Bell K. Medtronic's MiniMed 670G system approved by FDA for type 1 diabetes [Internet].FirstWord Medtech; 2016 Sep 28. [cited 2017 Feb 13]. Available from: http://www.firstwordmedtech.com/node/989872?tsid=28&region_id=2

11. Thabit H, Tauschmann M, Allen JM, Leelarathna L, Hartnell S, Wilinska ME, et al. Home Use of an Artificial Beta Cell in Type 1 Diabetes. N Engl J Med [Internet]. 2015 Nov 26 [cited 2017 Feb 13];373(22):2129-40. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4697362

12. Fradkin JE, Wallace JA, Akolkar B, Rodgers GP. Type 1 Diabetes--Reaping the Rewards of a Targeted Research Investment. Diabetes [Internet]. 2016 Feb [cited 2017 Jan 31];65(2):307-13. Available from: http://diabetes.diabetesjournals.org/content/diabetes/65/2/307.full.pdf

13. Chatterjee S, Davies MJ. Current management of diabetes mellitus and future directions in care. Postgrad Med J [Internet]. 2015 Nov [cited 2017 Jan 31];91(1081):612-21. Available from: http://pmj.bmj.com/content/postgradmedj/91/1081/612.full.pdf

14. Ly T, Roy A, Grosman B, Shin J, Campbell A, Monirabbasi S, et al. Hybrid closed-loop control using the medtronic 670G and Enlite3 system in type 1 diabetes at diabetes camp [abstract]. Diabetes Technol Ther. 2015;17:A-19. (Presented at 8th International Conference on Advanced Technologies and Treatments for Diabetes, ATTD 2015 Feb 18-21; Paris, France.).

15. Bergenstal RM, Garg S, Weinzimer SA, Buckingham BA, Bode BW, Tamborlane WV, et al. Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes. JAMA. 2016 Oct 4;316(13):1407-8.

16. Garg SK, Weinzimer SA, Tamborlane WV, Buckingham BA, Bode BW, Bailey TS, et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther. 2017 Mar;19(3):155-63.

17. Bergenstal RM, Weinzimer SA, Brazg R, Bailey TS, Buckingham B, Garg S, et al. Hybrid closed-loop (HCL) pivotal trial in type 1 diabetes [abstract]. Diabetologia. 2016;59(Suppl 1):S97. (Presented at 52nd Annual Meeting of the European Association for the Study of Diabetes, EASD 2016 Sep 12-16; Munich, Germany).

18. Medtronic Diabetes. Hybrid closed loop pivotal trial in type 1 diabetes. 2015 May 28 [cited 2017 Feb 6; Last updated: 2016 Oct 4]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02463097 Identifier: NCT02463097.

19. Roze S, Smith-Palmer J, Valentine WJ, Cook M, Jethwa M, de PS, et al. Long-term health economic benefits of sensor-augmented pump therapy vs continuous subcutaneous insulin infusion alone in type 1 diabetes: a U.K. perspective. J Med Econ. 2016;19(3):236-42.

20. Medtronic Diabetes. Safety evaluation of the hybrid closed loop (HCL) system in pediatric subjects with type 1 diabetes. 2016 Jan 16 [cited 2017 Feb 6; Last updated: 2016 Nov 23]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02660827 Identifier: NCT02660827.

21. Multi-center trial in adult and pediatric patients with type 1 diabetes using hybrid closed loop system at home. 2016 Apr 19 [cited 2017 Feb 21; Last updated: 2016 Oct 14]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02748018 Identifier: NCT02748018.

22. Haidar A, Smaoui MR, Legault L, Rabasa-Lhoret R. The role of glucagon in the artificial pancreas. The Lancet Diabetes and Endocrinology. 2016;4(6):476-9.

23. Iacovacci V, Ricotti L, Menciassi A, Dario P. The bioartificial pancreas (BAP): Biological, chemical and engineering challenges. Biochem Pharmacol. 2016;100:12-27.

24. Barnard K, Oliver N, Pinsker J, Astle A, Kerr D. Future artificial pancreas technology for type 1 diabetes: What do users want? [abstract]. Diabetes Technol Ther. 2015;17:A-107. (Presented at 8th International Conference on Advanced Technologies and Treatments for Diabetes, ATTD 2015 Feb 18-21; Paris France).

25. Franc S, Xhaard I, Orlando L, El MM, Petit MH, Randazzo C, et al. Do type 1 diabetic patients really want an artificial pancreas ? [abstract]. Diabetes Technol Ther. 2016;18 Suppl 1:A-54-A-55. (Presented at 9th International Conference on Advanced Technologies and Treatments for Diabetes, ATTD 2016 Feb 3-6; Milan, Italy).

26. Troncone A, Bonfanti R, Iafusco D, Rabbone I, Sabbion A, Schiaffini R, et al. The social acceptance of future artificial pancreas technology: Parents' perceptions of pedarpan (pediatrics artificial pancreas) [abstract]. Diabetes Technol Ther. 2016;18 Suppl 1:A-46-A-47. (Presented at 9th International Conference on Advanced Technologies and Treatments for Diabetes, ATTD 2016 Feb 3-6; Milan, Italy).

27. Heinemann L, Devries JH. Reimbursement for Continuous Glucose Monitoring. Diabetes Technol Ther [Internet]. 2016 Feb [cited 2017 Jan 30];18 Suppl 2:S248-S252. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4717510/pdf/dia.2015.0296.pdf

28. Rodbard D. Continuous Glucose Monitoring: A Review of Successes, Challenges, and Opportunities. Diabetes Technol Ther [Internet]. 2016 Feb [cited 2017 Jan 30];18 Suppl 2:S2-3-S2-13. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4717493/pdf/dia.2015.0417.pdf

29. Wilson DM. Clinical startup of the 670G closed loop insulin delivery system (670G startup). 2017 Jan 7 [cited 2017 Feb 21; Last updated: 2017 Jan 9]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT03017482 Identifier: NCT03017482.

30. HealthPartners Institute. A crossover study comparing two automated insulin delivery system algorithms in adolescents and young adults with type 1 diabetes. 2017 Jan 31 [cited 2017 Feb 21; Last updated: 2017 Feb 9]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT03040414 Identifier: NCT03040414