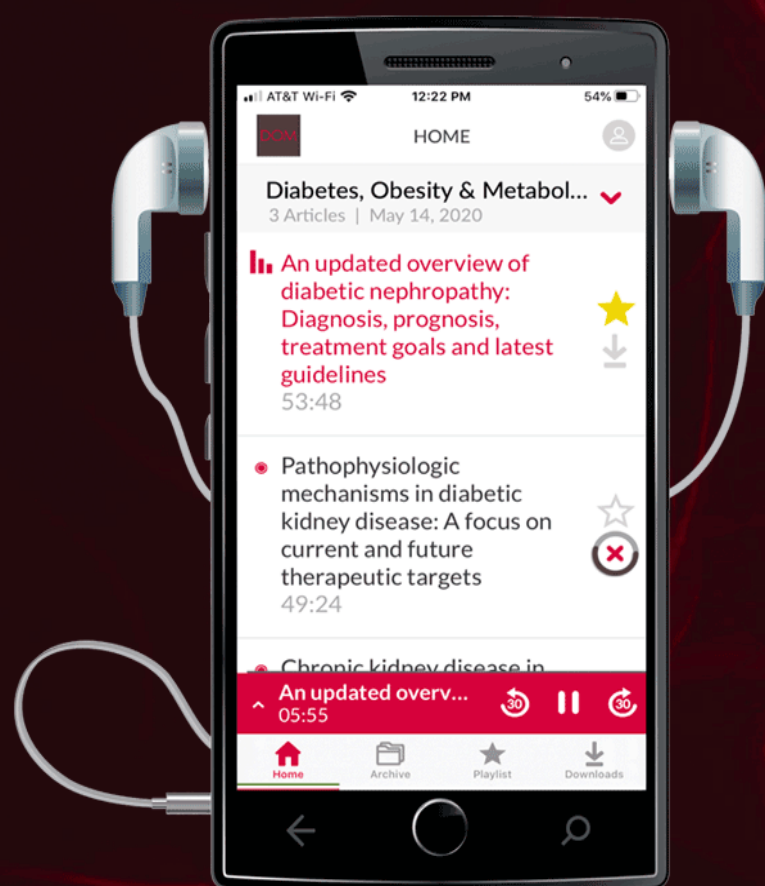


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Hybrid Closed-loop therapy: Where are we in 2021?

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Abstract

Hybrid closed-loop systems are characterised by the coexistence of algorithm driven automated insulin delivery combined with manual mealtime boluses. Used correctly, these insulin delivery systems offer better glucose control and reduced risk of hypoglycemia and represent the most advanced form of insulin delivery available for people with type 1 diabetes. This paper aims to compare the currently available commercial hybrid closed-loop systems in the UK: Medtronic 670G/780G, Tandem t:slim X2 Control IQ and CamAPS FX systems.

Medtronic 670G/780G systems use Guardian 3 sensor (7 day use, two to four calibrations / day) while Tandem and CamAPS systems use the calibration free Dexcom G6 sensor (10 days). CamAPS system is available as an android app while other two systems have the algorithm embedded in the insulin pump. During pivotal studies, depending on the study population and baseline HbA1c, these systems achieve % time spent in the target range 3.9 to 10 mmol/l (70 to 180mg/dl) from 65% to 76% with low burden of hypoglycemia. All three systems allow for a higher glucose target for announced exercise while the Tandem system offers an additional night time tighter target. The CamAPS system offers fully customisable glucose targets and is the only system licenced for use during pregnancy. Additional education is required for both users and healthcare professionals to harness the best performance from these systems as well as trouble shoot when 'auto-mode' exists occur. We provide consensus recommendations to develop pragmatic pathways to guide patients, clinicians and commissioners in making informed decisions on the appropriate use of the diabetes technology.

Introduction

Type 1 diabetes is a lifelong endocrine condition related to insulin-deficiency caused by pancreatic beta-cell dysfunction¹. People with type 1 diabetes therefore need to be able to self-adjust their insulin dose in order to achieve normoglycaemia and minimise the risk of micro and macrovascular complications. High blood glucose levels over time may cause complications associated with diabetes including damage to small and large blood vessels and nerves. Achieving glycaemic targets substantially reduces the risk of blindness, kidney failure, heart disease, stroke, and amputations^{2,3}. Diabetes remains responsible for a large number of additional deaths, with the greatest relative risk in younger people⁴. There has been major progress of available technology in type 1 diabetes to support diabetes management including insulin pump therapy, intermittently scanned glucose monitoring and real-time glucose monitoring, as well as increasing access to structured education in the context of advances in T1 diabetes care⁵. Despite this, less than 10% reach a target HbA1c level of 6.5% (48 mmol/mol), about 20% reach a level below 7.0% (53 mmol/mol) and less than 35% achieve a target of 7.5% (59 mmol/mol) or below based on the UK National Diabetes Audit⁶. Similarly in the USA type 1 diabetes exchange, The American Diabetes Association (ADA) HbA1c goal of <58 mmol/mol for youth was achieved by only 17% and the goal of <53 mmol/mol for adults by only 21%. Mean HbA1c levels changed little between 2010-2012 and 2016-2018, except in adolescents who had a higher mean HbA1c in 2016-2018⁷. Evolving technology offers the potential to improve glycaemic management reduce the above mentioned complications and the burden and risks of hypo & hyperglycaemia, while improving quality of life.



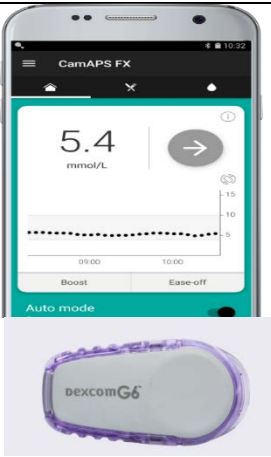
Closed-loop insulin delivery systems (also known as 'artificial pancreas' systems) take the technology to the next level by integrating continuous glucose monitoring with an insulin pump and an algorithm which automates insulin delivery. Hybrid closed-loop systems are characterised by the coexistence of automated insulin delivery (via the algorithm) and user-

initiated insulin delivery, for example, providing mealtime boluses. These insulin delivery systems offer better glucose control and reduced risk of hypoglycemia and represent the most advanced form of insulin delivery available for people with type 1 diabetes⁸⁻¹⁰. The objective of this paper is to compare the currently available commercial closed-loop systems in the UK thereby providing an up-to-date information for people living with type 1 diabetes and healthcare professionals to make an informed decision in a rapidly changing market.

Current closed-loop system availability in UK

Currently, three commercial closed-loop systems are available in the UK. In the order of introduction to UK market these are the Medtronic 670G system (and planned introduction of the 780G system in late 2020) (Minimed Medtronic, CA, USA) , CamAPS FX, developed by CamDiab Ltd (www.camdiab.com, Cambridge, UK), and Tandem Control IQ system (Tandem Inc, USA). Medtronic and Tandem systems have the algorithm embedded in the pump software. In contrast CamAPS FX is a smartphone app, a home-use medical device, that manages glucose levels continuously and autonomously via Bluetooth connection to compatible insulin pump and glucose sensor. In addition to the commercially available products, as outlined below, people with type 1 diabetes are also using self-built DIY Artificial Pancreas Systems. These products are unlicensed and users take responsibility for any risks associated with use. Table 1 shows a comparison of the three commercial hybrid-closed loop systems currently available in the UK.

Table 1. Current Commercial Hybrid Closed Loop Systems

	Medtronic 670G-Guardian 3 sensor Medtronic 780G-Guardian 3 sensor	Tandem t:slimX2-Dexcom G6 -Control IQ	CamAPS FX DanaRS-Dexcom G6
Hybrid Closed-Loop Systems			
Integrated pump	670G, 780G (coming soon)	Tandem t:slimX2	Dana RS Pump
Sensor	Guardian 3	Dexcom G6	Dexcom G6
Sensor duration	7 days	10 days	10 days
Number of fingersticks	4 to 6 a day, may be less for 780G	Rarely (Factory calibrated)	Rarely (Factory calibrated)
Licence	7 years and above	4 years and above	1 year and above
Pregnancy Licence	No	No	Yes
Algorithm used	Treat to target Proportional integral derivative (PID) with insulin feedback. 780G system also contain elements of MPC	Treat to range predictive algorithm	Treat to target Adaptive Model Predictive Control (MPC)
Adaptive Learning	Overall	Not reported by manufacturer	Overall, diurnal, meals
Customisable glucose target	670G: Target 6.7 mmol/l (120mg/dl) non-customisable (optional exercise target at 8.3 mmol/l, 150mg/dl). Correction target 8.3 mmol/l (150mg/dl)	Target range 6.2 (112.5mg/dl) to 8.9 mmol/l (160mg/dl) (sleep range 6.2 (112.5 mg/dl) to 6.7 mmol/l (120mg/dl), exercise range 7.8 (140mg/dl) to 8.9	Target 5.8 mmol/l (105 mg/dl) customisable between 4.4 (80mg/dl) and 11 mmol/l (200mg/dl). Optional activity target set.

	780G: Target 6.7, 6.1 or 5.5 mmol/l. Correction Target 6 mmol/l, exercise Target 8.3 mmol/l	mmol/mol)(160mg/dl) non-customisable.	
Exercise Mode	Yes	Yes	Yes
Boost Mode	No	No	Yes
Insulin compatibility	Rapid only	Rapid only	Rapid & ultra-rapid
Compatible downloading software	Carelink Manual downloading required for 670G. Automated app compatibility with 780G	Clarity (sensor data), Diasend, Manual downloading of pump required	Diasend Automated download
Automatic cloud storage of data	670G no 780G yes	Dexcom yes, pump no	Yes, full system
(%) Time in Range (3.9 to 10mM) achieved in pivotal trials	670G: Adolescents 67 % (Baseline A1c 7.7%) and Adults 74% (Baseline A1c 7.3%) ^{11, 12} 780g: Adolescents 73% (Baseline 7.6%) and Adults 75% (Baseline A1c 7.5%) ¹³	Adolescents and adults 71% (age range 14 to 71 years, baseline A1c 7.6%). Children 67% (age range 6 to 13 years, baseline A1c 7.7%) ^{14, 15}	Well-controlled adults (baseline A1c 6.9%) TIR 76% Poorly controlled adults & children (baseline A1c 8.3%) 65 - 68% ¹⁶⁻¹⁸
Waterproofing	Pump and transmitter are waterproof. Sensor is waterproof up to 12 feet for up to 24 hours	Pump is waterproof for up to 3 feet for 30 minutes and transmitter are waterproof for 8 feet	Pump is fully waterproof (IPX8) and transmitter is waterproof for 8 feet
Approximate Yearly Cost in UK NHS**	Pump=£612.50 Consumables=£1400 Medtronic Sensor =£3186 SMBG=£500 App=£0 Total Yearly Cost if new to pump=£5698.50	Pump=£838 Consumables=£1588 Dexcom G6 sensor=£2645 SMBG=£100 App=£0 Total Yearly Cost if new to pump=£5171	Pump=£575 Consumables=£1400 Dexcom G6 sensor=£2645 SMBG=£100 App=£840 Total Yearly Cost if new to pump=£5560
Yearly additional cost if already on pump	Cost of sensors £3186	Cost of sensors + extra cost of control IQ pump - savings from reduced SMBG) (2645+50-400)=£2295	Cost of sensors + extra cost of App - savings from reduced SMBG 2645+840-400=£3045

Advantages	Well established pump Robust training and support Strong clinical experience with 670G closed loop	Strong evidence base No need for fingerstick Attractive pump interface Online training for HCPs and users	Strong evidence base No need for fingerstick Wide age range and pregnancy licence Mobile app with customisable targets Bolusing from phone for added privacy Online training for HCPs and users
Disadvantages	Limited RCT evidence. Need for multiple finger-sticks, relatively conservative system Alarm fatigue with substantial discontinuation rates Auto mode exists with 670G which is likely to improve with 780G	Limited real-world clinical experience with the system as recently launched Cannot revert to previous basal suspend mode if closed-loop is not suitable Not compatible with faster-acting insulins Relies on users' basal rates, carb ratio and corrections	Limited real-world clinical experience with the system as recently launched App only available for Androids Need to carry the phone. Loss of Dexcom follow feature at present but "follow" planned later this year 2020.

**Prices are approximate in GBP based in the UK NHS and are correct at the time of publication, but these prices could vary in different countries.

Figure 1: Recommendation of hybrid-closed-loop therapy in the Diabetes Technology Pathway. Adapted from the Diabetes UK position statement

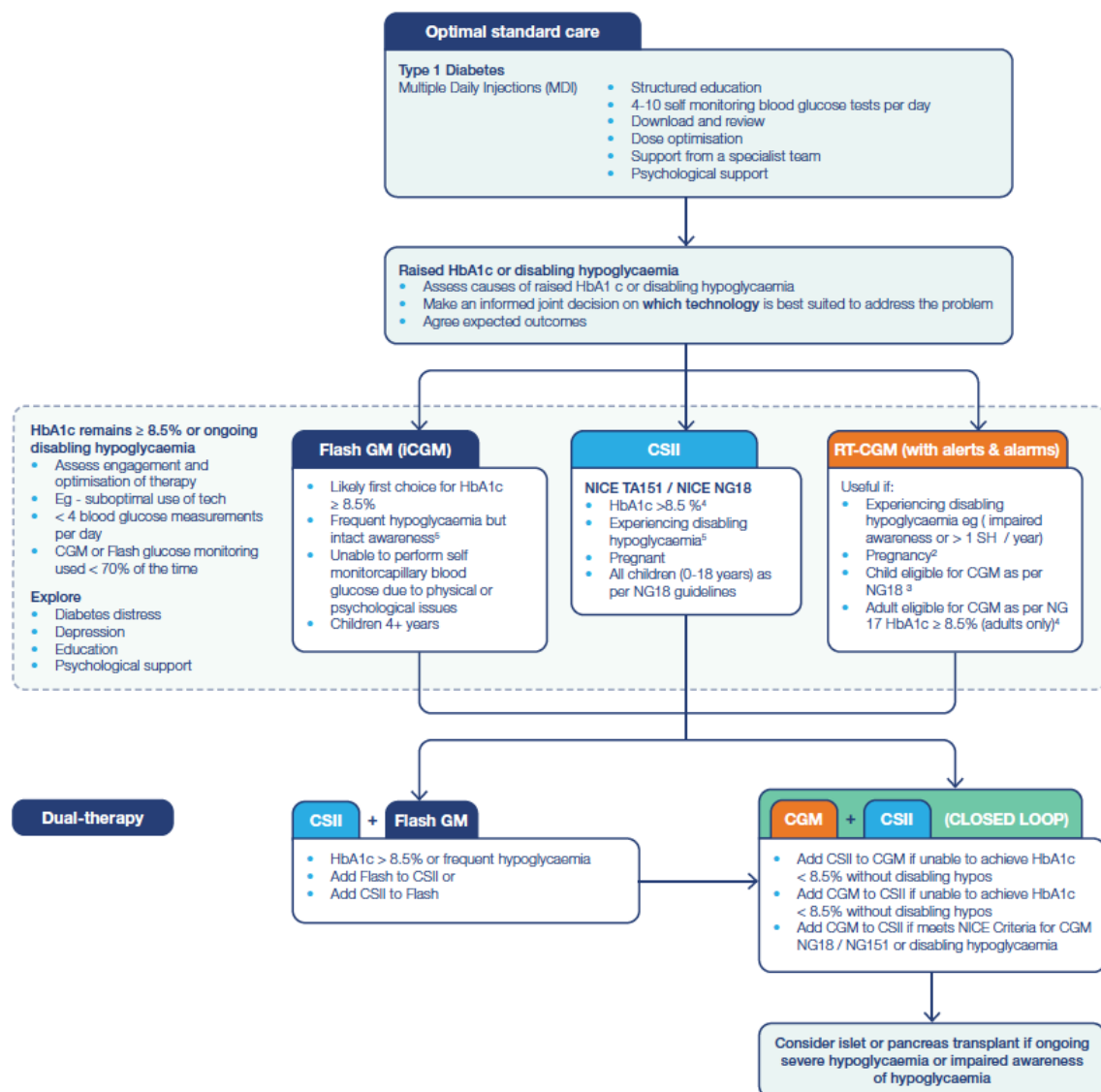


Figure 1 detail a pragmatic pathway with particular relevance to funding constraints within the UK healthcare system which is adapted from the Type 1 diabetes technology pathway¹⁹. At present, there is no international data to highlight the variations in the use of HCL systems and current global access is constrained by funding challenges.

Open Source Closed Loop systems

While commercial offerings have appeared in the past two years, there has been a vibrant community of people with type 1 diabetes writing their own insulin dosing algorithms that work with existing pump technology and releasing the code to open source repositories making it freely available for others to build²⁰⁻²³. These are commonly known as DIY Artificial Pancreas Systems (DIYAPS). As of writing, there are over 4,700 people worldwide using the various systems, with the preferred choice of system varying by geography depending on availability of different pumps. There are three systems available: OpenAPS (2015, running on small Linux computer); AndroidAPS (2017, running the same algorithm as OpenAPS on an Android phone) and Loop (2016, running on iPhone with RileyLink to talk to pumps)²⁰. In the UK, the most popular is AndroidAPS (used by 66% of users) due to the range of pumps and CGMs it works with. Various retrospective studies have shown that through the use of DIYAPS, there are reductions in HbA_{1c} and increases in Time in Range and that the glycemic benefit of DIYAPS is in reducing hyperglycemia without compromising the low occurrence of hypoglycemia²⁰.

Discussion

New and improved hybrid closed-loop technologies for the treatment of diabetes are continuing to emerge at an impressive rate. The Pivotal Omnipod Horizon™ Automated Glucose Control System clinical trials are currently underway and are due to be completed in December 2021²⁴ as well as the Insulin Only Bionic Pancreas (iLET) Pivotal Trial²⁵. Another closed-loop system current in use in France is the Diabeloop system^{26, 27}. The DBLG1 algorithm developed by Diabeloop is hosted on a dedicated handset and acts as a user interface. It is connected to a continuous glucose monitoring (CGM) and an insulin pump. The DBLG1 artificial intelligence analyzes the data in real time, while considering the patient's physiology,

history and data entries (meals or exercise) to determine the correct dose of insulin to administer.

At present, hybrid closed loops do not “automate” diabetes management but are likely to mostly benefit motivated individuals who are committed to maximise the clinical benefit. The need for appropriate education to maximise benefits of novel diabetes technology is well established.²⁸ Some education is common to most novel diabetes technology – for example need to count carbohydrates and deliver meal bolus with food. In addition there is also need for specific education with hybrid closed-loop systems: for example how to deal with & minimize with auto mode exists, dealing with connection problems & software issues and updates and how to safely use standard sensor augmented pump therapy at times when closed-loop is not working for what ever reasons^{29, 30}. Users and healthcare professionals also need to be educated about interpretation of data outputs from various closed-loop software systems and how to adjust existing pump settings based on closed-loop performance. Optimal user settings are more critical for some systems for example Tandem Control-IQ than other systems like CamAPS. For some individuals, such technology may be an additional burden of care as reported in some studies where there has been a high rate of “auto-mode” exits while using the hybrid closed loop functions^{31, 32}. It is important for future trials to focus on higher-risk populations such as those with persistently high HbA1c and/or low socioeconomic status to ensure that a skewed evidence base does not develop to exacerbate existing socioeconomic disparities in health outcomes and access to advanced technology. The success of diabetes technology implementation should emphasise on the importance of creating technology which places the lowest possible demands on the user and to minimise disparities in access. Ultimately, the goal in the future would be to provide full closed loop systems to all people living with type 1 diabetes.

Summary

As technology for insulin delivery systems continues to advance rapidly, healthcare professionals need to stay current to better guide their patients and provide the necessary education, support and patient choice when accessing appropriate technology. Digital revolutions in diabetes management will continue to progress, however digital gaps continue to exist with variations in care between areas of least and most socially deprived populations. This paper aims to develop robust and pragmatic pathways and information to guide clinicians and commissioners in making informed decisions on the most appropriate use of diabetes technology.

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