The road from intermittently scanned glucose monitoring to hybrid closed-loop systems: Part A. Keys to success: subject profiles, choice of systems, education

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Abstract: Managing type 1 diabetes (T1DM) is challenging and requires intensive glucose monitoring and titration of insulin in order to reduce the risk of complications. The use of continuous glucose monitoring (CGM) systems, either flash or intermittently scanned glucose monitoring (isCGM) or real-time (RT) CGM, has positively affected the management of type 1 diabetes with the potential to lower HbA1c, enhance time spent in range, reduce frequency and time spent in hypoglycemia and hyperglycemia, lower glycemic variability, and improve quality of life. In recent years, both CGM and pump technology have advanced, with improved functional features and integration, including low glucose suspend (LGS), predictive low glucose suspend (PLGS), and hybrid closed-loop (HCL) systems. In this review, we highlight the benefits and limitations of use of isCGM/RT-CGM for open-loop control and recent progress in closed-loop control systems. We also discuss different subject profiles for the different systems, and focus on educational aspects that are key to successful use of the systems.

Keywords: diabetes mellitus, continuous glucose monitoring, intermittently scanned glucose monitoring, hybrid closed loop, diabetes education

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Introduction

Living with type 1 diabetes mellitus (T1DM) is challenging and requires intensive glucose monitoring and titration of insulin in order to obtain near-normal glucose levels to reduce the risk of both acute (hypoglycemia, ketoacidosis) and chronic complications. However, changes in dietary intake and levels of physical activity, variability of subcutaneous insulin pharmacokinetics, circadian rhythm of insulin sensitivity, and menstrual cycle can all cause glucose excursions. The advent of continuous glucose monitoring (CGM) systems has transformed the way both patients and doctors manage diabetes nowadays. CGM systems, either intermittently scanned (isCGM) or real-time (RT-CGM), can provide a comprehensive picture of glucose profiles, allowing patients to make therapeutic adjustments to improve metabolic control. A growing body of evidence supports the use of CGM because it has the potential to lower HbA1c, enhance time spent in range, reduce frequency and time spent in hypoglycemia and hyperglycemia, lower glycemic variability, and improve quality of life (QoL), especially in subjects who wear the sensor at least 60–80% of the time (see also part B of this review).[1–26]

During recent years, both CGM and pump technology have advanced, with improved functional features and integration, including low glucose suspend (LGS), predictive low glucose suspend (PLGS) and even the first hybrid closed-loop (HCL) system. Therefore, lately, the use of isCGM/RT-CGM has expanded dramatically among individuals with T1DM. However, guidance on the choice of the system that best suits the clinical needs of the individual subject, and education about the use of these novel devices and guidance on the interpretation of real-time

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glucose values and trends is sparse.[27–32] isCGM can be used by patients using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII). However, for patients being treated by CSII RT-CGM devices may offer more benefits, certainly when both devices are integrated, which is called sensor-augmented pump (SAP) therapy. This is at present not feasible with either isCGM or stand-alone RT-CGM devices. LGS and PLGS systems have shown improvements in HbA1c, hypoglycemia, and QoL, and are particularly advantageous for people with frequent and severe hypoglycemia or hypoglycemia unawareness.[9–14,18–23] For brittle type 1 diabetic individuals, those with a dawn phenomenon, or with erratic life style, a HCL system (670G pump) with automated basal insulin delivery seems the best option if they are able to count carbs and receive proper education

This review addresses benefits and limitations of use of isCGM/RT-CGM for open-loop control and recent progress in closed-loop control systems; it describes different subject profiles for the different systems and focuses on educational aspects which are key to successful use of the systems.

Rationale for the use of isCGM and RT-CGM systems

Current isCGM/RT-CGM systems measure glucose in the interstitial fluid on a near-continuous basis (every 5 min), and unlike traditional blood glucose meters, display not only the actual glucose level (with a 5–15 min delay), but also the direction and speed of change of glucose levels *via* trend arrows, thereby anticipating future glucose levels. Some devices are equipped with alarms (cf. the next paragraph). Hereby, these devices enable patients to react immediately to prevent impending hypoglycemic or hyperglycemic events. They also provide insight into how food, activity, and illness affect glucose levels. isCGM/RT-CGM allows glycemic variability to be assessed and facilitates pattern recognition, thereby helping the patient (and physician) to optimize therapy and improve metabolic control.[27,33,34]

Key features of current isCGM and RT-CGM systems

CGM devices measure glucose in the subcutaneous interstitial fluid, either *via* enzymatic technology (glucose oxidase) using needle-type sensors either *via* fluorescence and photometrics using an implantable sensor (Eversense, Senseonics), and translate the values into blood glucose values. Important to realize is that glucose in interstitial fluid can lag 5–15 min behind the blood glucose, and even more when blood glucose levels are rapidly changing.

The analytical point accuracy of isCGM/CGM devices is evaluated by median absolute relative difference (MARD), which is the average of the sum of the differences between reference and sensor glucose values divided by the number of data points. The MARD of isCGM/CGM systems ranges between 9% and 13.6% (see Table 1). A MARD of ≤10% has been accepted for nonadjunctive use of these devices.[35] However, it is important to mention that this statistic does not account for the benefits of trend direction and rate of change information provided by isCGM/RT-CGM. For example, when a person with T1DM performs a capillary fingerstick before having to drive 45 min home, and sees a very accurate blood glucose value of 90 mg/dl (5 mmol/l), will this individual consume an extra snack before driving or not? In contrast, having trend information available from isCGM/RT-CGM, even with a less-point-accurate glucose value, gives much more clinical reliable information. If the trend is upward, no snack is needed. In contrast, fast-acting carbs are needed when rate-of-change is quickly decreasing (downward arrow(s)).

isCGM and RT-CGM have some features and functions in common such as display of current glucose values and trend information (graphs and arrows) on an external reader or mobile phone, but differences exist with regard to accuracy (as expressed by MARD), sensor lifespan, need for and number of calibrations per 24 h, presence of alarms, need for transmitter and transmitter life time, application methodology, connectivity with a pump, and costs (see Table 1).

Two sensors are factory-calibrated, the Freestyle Libre and the Dexcom G6, and do not require capillary fingersticks. The Dexcom G6, however, allows optional calibration to improve accuracy. The Freestyle Libre is the only sensor that requires active scanning for glucose values to be displayed. It is the only one without alarms or predictive alerts. SAP therapy is possible with the Enlite sensor, whereas the first HCL uses a

Table 1. Features of the different intermittently scanned (isCGM) and real-time continuous glucose monitoring (RT-CGM) devices.

	Freestyle libre	Dexcom G5	Dexcom G6	Enlite	Enlite	Enlite	Guardian	Eversense XL
Sensor life	14 days	7 days	10 days	6 days	6 days	6 days	7 days	6 months
Warm-up period	1 h (outside USA), 10 h (USA)	2 h	2 h	2 h	2 h	2 h	2 h	24 h
Number of calibrations	Factory calibrated	Every 12 h	Factory calibrated, but can calibrate if sensor is off-track	Every 12 h	Best results: 3–4×/day	Best results: 3–4×/day	Best results: 3–4×/day	Every 12 h
Trend arrows	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
High/low alarms	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Predictive alarms	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Real-time remote monitoring (data sharing)	No	Up to 5	Yes	Yes	No	No	No	Yes
Transmitter	/	Dexcom G5	Dexcom G6	Guardian connect	Guardian 2 Link	Minilink	Guardian 3 Link	Eversense XL
Transmitter warranty life	/	3 months	3 months	12 months	12 months	12 months	12 months	12 months
Sensor-augmented pump therapy	No	No	No	No	Medtronic 640 G	Medtronic Veo	Medtronic 670 G	No
MARD (%)	11.40%	9%	9%	13,60%	13.60%	13.60%	9.60%	9.40%
Accuracy affected by paracetamol	No	Yes	Yes	No	No	No	No	No
Methodology	Needle type based on glucose oxidase	Needle type based on glucose oxidase	Needle type based on glucose oxidase	Needle type based on glucose oxidase	Needle type based on glucose oxidase	Needle type based on glucose oxidase	Needle type based on glucose oxidase	Fluorescence
Application of sensor	Self	Self	Self	Self	Self	Self	Self	By health care specialist

MARD, median absolute relative difference.

Guarding 3 Link in combination with a Medtronic 670G pump.

Despite the highlighted benefits, the uptake of CGM and of SAP therapy remains limited. In addition to financial issues (limited reimbursement), reasons for this situation include the short lifespan of the sensor, the perceived burden of frequent insertions with needle-type sensors, the likelihood of accidental sensor dislocation, the occurrence of skin reactions to the adhesive in 3–10% of subjects, the fear of pain or discomfort, or privacy reasons (keep their diabetes hidden).[36,37] Unfortunately, these challenges relate directly to the core design of any needle-type CGM system based on glucose oxidation. A novel

option is a long-term implantable RT-CGM device, the Eversense.[38,39] Application of the Eversense sensor can, however, not be done by the patient themselves. On the other hand, individuals with cheiroarthropathy, low dexterity, or only one arm can now be helped by the Eversense. Other strengths of the Eversense are its longevity (up to 180 days), the fact that the sensor cannot be accidentally dislodged, and that subjects developing an allergic reaction to adhesives (often containing isobornyl acrylate) can use Eversense.

In summary, each system has its limitations but also unique features that should be considered when helping patients to select the system that best serves their needs.

Indications for isCGM and RT-CGM: subject profiles

isCGM should be considered for all persons with T1DM and T2DM on multiple daily insulin injections. Based on professional experience within our team of diabetologists and diabetes educators, discussions with other diabetologists, previously published recommendations, and personal experience, we try to give guidance on selection of appropriate devices for the individual patient.[27–32,40,41] Appropriate candidates for isCGM/RT-CGM therapy include the following individuals.

- Not achieving target HbA1c levels (HbA1c ≥7.5%) despite maximal efforts and motivation.
- Daily wide glycemic fluctuations (brittle diabetes).
- Frequent hypoglycemic episodes:
  ○ nocturnal hypoglycemia;
  ○ hypoglycemia unawareness;
  ○ frequent severe hypoglycemic spells;
  ○ high-risk profession where hypoglycemic avoidance is highly recommended.
- Pregnancy and pregnancy wish.
- Sports.
- Young children,[41,42] due to:
  ○ decreased ability to express needs or signal hypoglycemic or hyperglycemic events;
  ○ unpredictable eating habits;
  ○ fear of hypoglycemia in parents or caregivers, particularly nocturnal hypoglycemia, thereby necessitating the need to wake up several times to monitor glucose values.

Not all individuals have the same needs, and some systems are better suited for certain profiles (see Table 2). Subjects who, despite maximal efforts and motivation, are not achieving target HbA1c levels (HbA1c ≥7.5%) or experience daily wide glycemic fluctuations [brittle diabetes; coefficient of variation (CV) ≥36%] are candidates for isCGM/RT-CGM, but also for a pump. Several standalone RT-CGM devices exist, but the integration of both RT-CGM and CSII, called SAP therapy, is the next step. Candidates for PLGS include those listed above, but also those experiencing frequent hypoglycemic events, severe hypoglycemic events with/without coma, hypoglycemia unawareness, preconception, and pregnancy. HCL systems are particularly suited for those patients who have a very brittle diabetes, a significant dawn phenomenon, or erratic lifestyle. However, they need to be able to count carbs and willing to perform fingersticks to calibrate the sensor. In addition, the 670G is probably not the best option for pregnancy, because more stringent glycemic targets are aspired. Furthermore, the 670G is not licensed to be used in those needing ≤8 units of insulin a day and in the very young (aged <7 years).

Very young children often are unable to adequately communicate needs or feelings (e.g. hypoglycemic events). Therefore, parents or caregivers may adopt a strategy of constant vigilance.[41] Indeed, 90% of hypoglycemic events in infants and toddlers, documented by blinded CGM, occurred without being detected by the caregivers.[43] In addition, unpredictable eating habits may cause large glycemic fluctuations (with a danger of hypoglycemia in the case of insufficient carbohydrate intake). Importantly, many parents fear nocturnal hypoglycemia and wake up several times to monitor glucose values of their child. These are all indications specific for children.[41] Evidently, education of parents, school nurses, teachers, and caregivers is needed to obtain the full benefits of CGM.[42]

Limited evidence is available for the use of isCGM in the pediatric population. It can be used as of age 4 years. Paradoxically, most advances in technology for diabetes have increased the burden of disease. HCL systems do not cure diabetes but may have the potential to alleviate some of the daily burden of disease,

Table 2. Choices of the different isCGM/CGM systems in patients on multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII).

Insulin administration	MDI	MDI	MDI	MDI	CSII	CSII	CSII	CSII
Glucose monitoring	SMBG	isCGM	CGM	CGM	CGM	LGS	PLGS	HCL
Patient characteristics								
HbA1c	Good	Moderate	Moderate	Moderate	Improvement needed	Improvement needed	Improvement needed	Improvement needed
Glucose variability	Low	Moderate	Moderate	Moderate	Moderate	High	High	High
Hypo unaware	No	No	Sometimes	Sometimes	Sometimes	frequent	Yes	Yes
Intimacy	Yes	Yes	Yes	Yes	?	?	?	?
Allergy	No	3%	Rare	No	Rare	Rare	Rare	Rare
Sensor	/	Freestyle Libre	Dexcom G5, G6 / Enlite	Eversense	Dexcom G5, G6 / Eversense / Enlite	Enlite	Enlite	Enlite
Transmitter	/	/	Guardian connect for Enlite	/	Guardian connect for Enlite	Minilink	Guardian 2 Link	Guardian 3 Link
CSII type	/	/	/	/	Roche Accuchek / Animas Vibe / Tandem t:slim X2	Paradigm	640G	670G

CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; HCL, hybrid closed loop; isCGM, intermittently scanned glucose monitoring; LGS, low glucose suspend; MDI, multiple daily injections; PLGS, predictive low glucose suspend; SMBG, self-monitoring of blood glucose.

Table 3. Meaning of the arrows in the different continuous glucose monitoring devices.

Devices	Freestyle Libre and Eversense		Dexcom G5/G6		Guardian connect	
Arrow	Meaning	Arrow	Meaning	Arrow	Meaning
		↑↑	Increasing >3 mg/dl/min or 0.17 mmol/l/min	↑↑↑	Increasing >3 mg/dl/min or 0.17 mmol/l/min
↑	Increasing >2 mg/dl/min or >0.1 mmol/l/min	↑	Increasing 2–3 mg/dl/min or 0.1–0.17 mmol/l/min	↑↑	Increasing 2–3 mg/dl/min or 0.1–0.17 mmol/l/min
↗	Increasing 1–2 mg/dl/min or 0.06–0.1 mmol/l/min	↗	Increasing 1–2 mg/dl/min or 0.06–0.1 mmol/l/min	↑	Increasing 1–2 mg/dl/min or 0.06–0.1 mmol/l/min
→	Stable	→	Stable	-	Stable
↘	Decreasing 1–2 mg/dl/min or 0.06–0.1 mmol/l/min	↘	Decreasing 1–2 mg/dl/min or 0.06–0.1 mmol/l/min	↓	Decreasing 1–2 mg/dl/min or 0.06–0.1 mmol/l/min
↓	Decreasing >2 mg/dl/min or >0.1 mmol/l/min	↓	Decreasing 2–3 mg/dl/min or 0.1–0.17 mmol/l/min	↓↓	Decreasing 2–3 mg/dl/min or 0.1–0.17 mmol/l/min
		↓↓	Decreasing >3 mg/dl/min or 0.17 mmol/l/min	↓↓↓	Decreasing >3 mg/dl/min or 0.17 mmol/l/min

thereby allowing pediatric patients to fulfill the primary goal of childhood, being a child.[41] However, as mentioned above, the 670G system cannot be used in those needing ≤8 units of insulin a day and is not licensed to be used in the very young (age <7 years).

Subjects with high diabetes distress, low self-efficacy, who want to keep their diabetes hidden, have less-positive technology attitudes, are unwilling to perform capillary blood glucose measurements to calibrate the system, or are not capable or not willing to interpret the huge amount of continuous data from CGM devices, are less inclined to use RT-CGM and probably not good candidates.[44]

Educational aspects

Not only persons with diabetes and/or partners/parents need to be educated but also physicians and diabetes educators. Education consists of technological aspects and data interpretation. Key aspects of successful implementation of all these systems are engagement and education of the patient (and the diabetes team).

Technological aspects:

- sensor application/insertion;
- sensor calibration;
- changing batteries/charging sensor;
- connecting sensor with the reader/mobile phone/pump.

Data interpretation:

- lag time, particularly when correcting hypoglycemia;
- trend arrows (the meaning of trend arrows differs between devices, see Table 3);
- high/low alarms;
- predictive or rate of change alarms;
- how carbs and physical activity affect glucose profiles.

General educational aspects:

- correction of hypoglycemia;
- effect of physical activity;
- carbohydrate counting, essential when using HCL systems;
- action profile of insulin/insulin on board;
- bolus wizard in pump.

Persons with diabetes need to be trained to be able to perform sensor insertion, calibration, and real-time data interpretation. They must understand the meaning of trends, alarms, predictive alerts to be able to respond to the isCGM/

RT-CGM data they see. Carb counting must be reeducated to successfully use the HCL system. This is of paramount importance.[28]

Setting the alarms is recommended to be done in stages. At the start, it is prudent to only set up hypoglycemia alerts, and no hyperglycemia alarms, and even no predictive low alerts, in order to avoid having too many alarms, which may lead to alarm fatigue. In a next stage, predictive low-glucose alerts and high-glucose alerts can be turned on, with wide thresholds in the beginning, and narrowing down at more advanced stages, based on the individual's needs.

isCGM or flash glucose monitoring
The use of the Freestyle Libre has expanded tremendously in the last 2 years, particularly in subjects treated by MDI. This device provides current glucose values, trend information indicating the direction and velocity of changing glucose, and glucose data of the previous 8 h. It does not, however, have automatic alarms, and requires active scanning by the individual to be able to use it to the full potential.

In a randomized controlled study of 328 well-educated and motivated persons with T1DM, with a baseline HbA1c ≤7.5%, the use of Freestyle Libre reduced the time spent in hypoglycemia by 38% while maintaining HbA1c, and improved user satisfaction.[6] In a Belgian observational study of 1913 T1DM subjects, use of isGCM resulted in high treatment satisfaction, fewer hospitalizations for acute diabetes complications, less-severe hypoglycemia, and less work absenteeism, whereas HbA_{1c} improvement was mainly seen in those with worse control at baseline.[45]

At the start of this device, however, patients need to be educated, not only about technical aspects, but also about lag time and possible differences between capillary glycemia and intermittently scanned glucose data measured in the interstitial fluid, particularly at times of rapidly changing glycemia. They must understand the meaning of trends to be able to adjust rapid-acting insulin doses for correction boluses or for hypoglycemia prevention or correction. Insulin dose adjustments need to be individualized based on insulin sensitivity, target glycemia, planned food intake (quantity and composition) and physical activity

level, directionality of the trend arrow, and insulin on board.

Although there are no rules for scanning frequency, more frequent scanning is associated with better results in terms of HbA1c and frequency of hypoglycemia. A gap in data exists when the time between to scans exceeds 8 h. Routine scanning is advised prior to every meal, and 2 h postprandially, before going to bed, and when waking up in the night.

The Freestyle Libre 14 day device is officially not approved to be used in a nonadjunctive way, because the MARD is above 10%. However, in real life, many patients no longer conduct a fingerstick. However, it is important to stress that in certain conditions, a confirmatory fingerstick is mandatory. These situations include:

- suspicion of an inaccurate reading;
- experiencing symptoms (hypoglycemia or hyperglycemia) that do not match sensor glucose readings;
- when correcting a hypoglycemic event (due to the lag time and danger of overcorrecting);
- when reader displays 'high', meaning a glucose value >500 mg/dl (27.8 mmol/l);
- during the first 10 h of wearing the sensor (owing to lower accuracy).

The direction of the trend arrows allows patients to anticipate future glucose concentrations and this information can be used proactively to adjust therapy, thereby trying to prevent hypoglycemic or hyperglycemic events. A proposal of premeal insulin dose adjustment, based on trend arrows and insulin sensitivity is shown in Table 4. This is based on personal and professional experience within our team of diabetologists and diabetes educators, discussions with other diabetologists, and previously published recommendations.[28–32,42] In addition, one should take the lag time (of approximately 10 min) into account (e.g. Table 5: situation 5).

In this article, educational guidance is proposed, consisting of several clinical situations which occur commonly in daily life (see Table 5), thereby facilitating individualized recommendations. It is recommended to discuss these situations with your

Table 4. Proposal of insulin dose adjustments based on rate of change in glucose and on correction factor.

Rate of change in glucose	Insulin dose adjustments depending on correction factor			
in mg/dl	<25	25–49	50–74	≥75
increasing >2 mg/dl/min	+ 3	+ 2	+ 1	+ 1
increasing 1–2 mg/dl/min	+ 2	+ 1	+ 1	+ 1
stable	=	=	=	=
decreasing 1–2 mg/dl/min	– 2	– 1	– 1	– 1
decreasing >2 mg/dl/min	– 3	– 2	– 2	– 1
Rate of change in glucose	**Insulin dose adjustments depending on correction factor**			
in mmol/l	<1.4	1.4–2.7	2.8–4.1	≥4.2
increasing >0.1 mmol/l/min	+ 3	+ 2	+ 1	+ 1
increasing 0.06–0.1 mmol/l/min	+ 2	+ 1	+ 1	+ 1
stable	=	=	=	=
decreasing 0.06–0.1 mmol/l/min	– 2	– 1	– 1	– 1
decreasing >0.1 mmol/l/min	– 3	– 2	– 2	– 1

diabetes team and the patient. Main points are to wait at least 2 h after a meal bolus before administering a correction bolus to avoid insulin stacking, and to perform a confirmatory capillary blood fingerstick in the case of prolonged hypoglycemia or in the case of 'high' values, and rescanning after taking corrective actions. Patients should know that the glucose-lowering action of rapid-acting insulin can take up to 90–120 min to peak and may work for 4–5 h. In addition, in the case of hypoglycemia, it will take more 15–30 min before the corrective effects of fast acting carbohydrates become visible on isCGM/RT-CGM monitors. Recommendations on the use of CGM during exercise are beyond the scope of this article.

Data analysis of isCGM/CGM reports

For both persons with diabetes and health care professionals software is available for retrospective data review and analysis. The Ambulatory Glucose Profile (AGP) is very useful.[46] It provides a standardized visualization of glucose data that is generated from isCGM or CGM over several days (e.g. 14 or 28 days) to up to 3 months, that is collapsed into a single 24-h period, creating a 'modal day'. This view reveals data capture, median glucose levels, 25–75th percentile, 10–90th percentile, enabling underlying patterns in glucose variability to detected and HbA1c to be estimated.

Correct interpretation is paramount. A structured assessment is proposed, providing guidance about how to interpret and analyze the AGP report.

1. Check for adequate data:
- at least 14 days to allow for patterns and variability to be visualized;
- number of scans in case of Freestyle Libre;
- percentage capture or sensor wear.

2. Look for patterns of low glucose:
- fasting *versus* postprandial (after every meal of one specific meal);
- Carb counting correct? Insulin–carb ratio needs adaptation?
- Correction bolus correct? Insulin sensitivity factor correct?
- After physical activity?
- Insulin stacking from aggressive correction of previous hyperglycemia?

Table 5. Educational guidance in seven clinical situations.

	Situation	Reflection	Immediate action	Future action
1	1 h after a meal: glucose is 250 mg/dl (14 mmol/l) with an 45° increasing arrow	Forgot to inject?	In case you forgot to inject: inject usual dose immediately	Consider injecting 10–30 min before the meal
		Wrong injection technique: problems with pen or pump / lipohypertrophic injection site?	In other cases: scan 2 h after meal, do not give a correction bolus as glucose levels peak 60–90 min after the meal and full glucose-lowering action of insulin takes approx. 60 min	Consider consuming a less high-glycemic index rich meal
		Glycemia premeal?	If still high 2 h postmeal: correction bolus	Consider faster-acting insulin
		Ate more carbs than initially thought?		Be careful about augmenting premeal dose: risk of late postprandial hypo
2	90 min before a meal: glucose is 250 mg/dl (14 mmol/l) with flat arrow	Ate a snack without injecting?	Consider a full correction bolus, but be careful (previous meal is already digested, exercise planned?)	If this occurs frequently: consider augmenting insulin dose by 20% prior to the previous meal
		Overcorrection of previous hypo?	Before the next meal (90 min later) reduce usual bolus by 25% because glucose-lowering action of correction bolus is still ongoing	
		Any exercise planned?		
3	Before bedtime, glucose is 90 mg/dl (5 mmol/l) with a flat arrow	Done physical activity?	In the case of physical activity: eat snack (fruit, yoghourt)	If this occurs frequently: consider lowering pre-dinner fast-acting insulin by 20%
		Look at profile of previous nights	In case of hypos the previous nights: eat snack	In the case of nocturnal hypos: cf. situation 4
		Previous nights: hypos or not?	In other cases: be reassured	
		Lower carb content at dinner?		
4	At waking up, patient notices nocturnal hypoglycemia	Did the hypo occur early (<5 h after dinner) or late in the night?	Upon awakening: no immediate action required	In the case of frequent nocturnal hypos:
		In case of early hypo: lower carb intake than usual? Physical activity?		lower basal insulin dose by 20% if hypo's occur in the second part of the night
		In case of late hypo: too much basal insulin? Physical activity?		Lower bolus insulin by 20% prior to evening meal in hypo's occur in the first part of the night
		Drank alcohol?		

(Continued)

Table 5. (Continued)

	Situation	Reflection	Immediate action	Future action
5	2h after meal: glucose is 90 mg/dl (5 mmol/l) with a 90° decreasing arrow	Done exercise?	Consider this as a hypo (due to lag time: actual glucose is minimum 30 mg/dl lower)	If this frequently occurs, consider reducing bolus insulin by 20% prior to the previous meal
		Ate fewer carbs?	Correct hypo: 10–15 g of fast-acting carbs, and a snack	
		Injected too much insulin?	Rescan in 15 min	
			Doublecheck using fingerstick: avoid overcorrection (due to prolonged hypo values using CGM because of lag time)	
6	Glucose level is 40 mg/dl (2.2 mmol/l), but patient does not feel hypoglycemic	Hypo unaware?	Rescan to check accuracy	Take blood strips and glucometer with you
		Drank alcohol or started beta-blocker, masking symptoms?	Perform fingerstick to check/ confirm	Discuss hypo awareness with doctor
		Done physical activity?	If hypo is confirmed: treat as hypo: 10–15 g fast-acting carbs and a snack	
7	CGM shows 'high'	Forgot to inject?	High means > 500 mg/dl (27,8 mmol/l)	Accustomise yourself with "sick day rules"
		Wrong injection technique: problems with pen or pump / lipohypertrophic injection site?	Doublecheck using fingerstick	
		Ate more carbs than initially thought?	If correct reading: use 'sick day rules': drink water, check ketones, inject correction bolus	
		Overcorrected a previous hypo?	If the situation does not improve: call your diabetes team	
		Feel sick? Vomiting?		

3. Look for patterns of high glucose levels:
- nocturnal *versus* throughout the day;
- postprandial (after every meal of after one specific meal);
- before going to bed;
- snacking; defensive eating (fear of hypo at night);
- too many carbs, improper insulin–carb ratio.

4. Look for areas of wide glucose variability (width of the interquartile range):
- timing and amount;
- fluctuating meal patterns/times;
- different times of physical activity.

5. Mark up the AGP report: note factors that may affect the management plan:

- note time of insulin injections, food intake, physical activity;
- working days *versus* weekend days; shift work;
- stressors, illness, menses;

6. Ask the patient: 'what do you see?': shared decision making; personalized medicine, visual learning.

7. Compare with past AGP and reinforce successful strategies:
- better stability, less variability helps to build confidence;
- compare improvement of time in range, reduction of time in hypo/hyper;
- check eA1c or GMI (glucose management indicator).

8. Agree on action plan with patient, shared decision making:
- set goals; time in range (personalize);
- empower the person with diabetes.

Not only standardized analysis, but reporting is also important. Standardized tools such as the AGP (Abbott, Medtronic Carelink), Pattern Snapshot (Medtronic), and Clarity (Dexcom) are available. An international consensus gives recommendations to report on 14 metrics.[47]

- Data sufficiency:
  - minimum 2 weeks;
  - 70–80% of CGM readings over a 2-week period.
- Mean glucose.
- Percentages of time
  - <54 mg/dl (<3 mmol/l);
  - <70–54 mg/dl (<3.9–3.0 mmol/l) (target <3%);
  - 70–180 mg/dl (3.9–10 mmol/l) (target >70%) and 70–140 mg/dl (3.9–7.8 mmol/l);
  - >180 mg/dl (>10 mmol/l);
  - >250 mg/dl (>13.9 mmol/l).
- Glycemic variability, reported as CV (target <36%) and standard deviation.
- Estimated A1c or glucose management indicator.
- Data for glucose metrics reported in three time blocks (sleep, wake, 24 h).
- Episodes of hypoglycemia and hyperglycemia.
- Area under the curve for research purposes.

- Low and high blood glucose index as risk markers for hypoglycemia and hyperglycemia.

The road towards the artificial pancreas

Currently, a number of subjects use standalone RT-CGM or even isCGM devices in combination with a pump, without the integration of CGM data into an insulin-delivery algorithm. This practice will become obsolete in the very near future. Nevertheless, randomized controlled trials (RCTs) and observational data evaluating standalone RT-CGM have shown improvements in HbA1c, both in children and adults with T1DM treated with either MDI or CSII. In addition, time spent in hypoglycemia is shortened.[1–4,24–26] The benefits were seen in those who used their device on a regular basis (usually >60–80% of the time) and with higher baseline HbA1c values.[1,2]

In the last decade, insulin pumps (CSII) and RT-CGM systems have been combined in SAP therapy, the first step towards the artificial pancreas. The first step towards the artificial pancreas was the development of a LGS system (Medtronic Paradigm Veo). Here patients can see the glucose readings and trends on the display of the pump, and the proportional–integral–derivative (PID) algorithm suspends insulin delivery for up to 2 h once the preset hypoglycemic threshold is reached. The threshold can be individualized (60–70–80 mg/dl). The ASPIRE-in home study of 247 type 1 diabetic subjects demonstrated a 37% reduction in area under the curve for nocturnal hypoglycemia, while maintaining HbA1c.[9]

The second step is a PLGS system (Medtronic 640G) where insulin delivery is suspended when the algorithm predicts, based on CGM data, hypoglycemia within the next 30 min, thereby preventing hypoglycemic events. In RCTs but also in observational studies time spent in hypoglycemia decreased, without an increase in HbA1c.[13,14,48] In the Belgian RESCUE trial, not only time in hypoglycemia was reduced by 30%, but HbA1c (–0.3%) and QoL improved as well.[26] Importantly, the rates of hospitalization for severe hypoglycemia or for diabetic ketoacidosis (DKA) decreased substantially (from 16% in the year preceding CGM to 4% the following year), with a decrease in admission days from 54 to 18 per 100 patient years.[26] In

addition to the Medtronic 640G system, Tandem's t:slim X2™ insulin pump (Tandem Diabetes Care) is now integrated with a Dexcom G5 sensor and marketed with a predictive suspend feature also reducing time in hypoglycemia.[19]

For RT-CGM, both RCTs and observational studies reported greater treatment satisfaction with the use of RT-CGM regardless of MDI or CSII use.[11–14,16–18,20,21,26,49] In subjects with hypoglycemia unawareness, the use of CGM decreased fear of hypoglycemia, improved hypoglycemia-related confidence, especially in social situations, contributing to greater well-being and QoL; and increased treatment satisfaction.[8,11,20,21] In children RT-CGM use did not significantly change children's self-reports.[49] In parents of children with T1DM, RT-CGM with remote control increased parents' proxy rates on children's QoL, decreased familial distress and increased parental sleep without changes in children's self-report on QoL.[49]

The third step consists of a HCL system. Three types of algorithms have been tested: PID, model-predictive control (MPC), and fuzzy-logic controller (FL).[50] In the Medtronic 670G HCL system, basal insulin is automatically controlled by the system day and night, according to sensor glucose, targeting a fixed target of 120 mg/dl (6.7 mmol/l) without user input, using a PID algorithm.[51] At present, it is the only US Food and Drug Administration (FDA)-approved system. The user can only adjust active insulin time (preferably 3–4 h), insulin–carb ratio, and target glucose (120 *versus* 150 mg/dl in case of physical activity). Subjects have to enter the carbohydrate content of meals, bolus preprandially (owing to the relatively slow action profile of current rapid-acting insulin analogs), and calibrate the sensor at least twice a day (preferably three or four times daily). Only normal wave boluses can be delivered in function of preset insulin–carb ratio, and insulin sensitivity is automatically adjusted every 24 h by the system. However, meals still need to be announced and this system has not yet been tested during exercise. Another limitation is the inability to deliver square wave or dual boluses for complex meals with low glycemic index or with a high protein or fat content. This system might also not be ideal for diabetic women with pregnancy wish or currently pregnant because preprandial glucose levels <120 mg/dl are being targeted. Two to four calibrations *via* fingersticks are required to ensure good accuracy (MARD

<10%). When calibrating every 12 h a MARD of 10.3% was observed, further improving to 9.6% when calibrating three or four times a day.[52] The device can also function in manual mode with the same features as the 640G pump. Indeed, patients must be aware that in the case of prolonged hypoglycemia (owing to overestimation of carbohydrate content of the meal or excessive exercise), or prolonged hyperglycemia (underestimation of carbohydrate content, forgotten bolus), or loss of sensor signal, or maximum insulin dose delivered, the pump can switch to manual mode.

A pivotal trial of 124 subjects with T1DM (94 adults, 30 adolescents) who wore the system for 3 months established the safety, showed a reduction in HbA1c (from 7.4% to 6.9%) and time in range (70–180 mg/dl) increased from 67% to 72%. No severe hypoglycemic events were reported.[22] A RCT is underway.[53]

In practice, this HCL system needs to be started in manual mode, where basal insulin rates, glucose targets, insulin–carb ratios, insulin sensitivity factor, active insulin time, and alarms are preset, before transitioning to the automated basal delivery mode (automode). The new pump needs at least 48 h of data to be able to function in automode. However, before initiating the person onto automode in our clinic, we appropriately train the patients, particularly on carb counting, and let them be in manual mode for 1 week. The same protocol has also been used by others.[51,54,55] Patients need to upload their data to their Carelink personal account and allow the diabetologist or diabetes educator to review their data. In general, the insulin–carb ratio needs to be strengthened by 10–15%, and basal rates are being decreased (automatically) by 10–15%. The system is self-learning and in the beginning conservative correction boluses are being advised. The user can only accept or deny to administer this bolus, but cannot adjust the dose of the bolus. Some individuals are frustrated in the beginning and try to outsmart the system by administering 'phantom or fake carbs'. The patient is misleading the system by informing it that they are going to consume carbs, when in fact they are not. This enables them to administer extra boluses. However, this practice needs to be strongly discouraged because the system is self-learning and will adapt the insulin sensitivity or correction factor every 24 h. In addition, the administration of fake carbs can then lead to hypoglycemia. For complex meals with a high fat

or protein and low carb content, we advise our patients to administer half of the bolus before and half of it after the meal. Others advise to increase the total carb amount by 30% to accommodate increased insulin requirements dictated by the meal and to divide the bolus into 30–40% upfront and 60–70% after consuming the meal.[54] In the case of prolonged aerobic exercise (>60 min), patients are advised to decrease the bolus by 50% and to enter 50% of the calculated carbs to be eaten for the meal prior to exercise. The system thus requires active patient engagement, but when one respects the rules, results are promising. Thus, this first HCL system with automated basal insulin delivery aimed at a glycemia of 120 mg/dl, provides further benefits with more time spent in range. It is a step towards the artificial beta-cell or sometimes called the artificial pancreas.

Another investigational system includes a modified version of OmniPod, the Dexcom G4 505 Share® AP System, and a personalized MPC algorithm running on a tablet computer. Data were recently published on the safety and feasibility of this combination.[56] However, longer-term studies will be needed to assess the safety and performance of the algorithm under free-living conditions with extended use.

Other HCL systems and fully closed-loop systems have been tested, gradually increasing independence of the user, from the hospital to clinical research units, to diabetes camps, to at-home conditions, proving its value.[57–67] The description of these systems is beyond the scope of this article because their introduction in clinical practice at this time is sparse.

Risks and limitations of current isCGM/RT-CGM systems

Despite all the significant advances that modern technology brings along, risks and limitations also need to be discussed.

In a 12-week RCT comparing HCL with SAP in 86 subjects with T1DM 6 years or older, one episode of DKA was observed in the HCL group owing to infusion set failure.[23] In real-world observational data, there is no sign of increased risk of DKA. In the T1D Exchange clinic registry, in 2014, when still using older CGM devices, there was no increased risk of severe hypoglycemia or

DKA.[25] In the Belgian RESCUE trial, rates of hospitalization for severe hypoglycemia or for DKA decreased substantially (from 16% in the year preceding RT-CGM to 4% the following year), with a decrease in admission days from 54 to 18 per 100 patient years.[26] In 2017, Medtronic began marketing the 670G insulin pump with Guardian 3 sensor. Initial safety trials showed no occurrence of DKA or hypoglycemia.[51] Thus, when using SAP, the chance of DKA is still present, but rare. As the sensor will sound an alert in the case of profound hyperglycemia, the chances of DKA might be less than in patients using CSII and SMBG. Reports on CGM malfunction are almost nonexistent. These should be reported in future publications. Some technical issues are episodic differences in sensor performance.[40] However, on the other hand, when a sensor malfunctions, it can be replaced by another.

Furthermore, barriers to its widespread adoption in real life still exist. These relate to the relative short lifespan of most sensors, thereby requiring frequent replacement, issues about suboptimal accuracy at hypoglycemic values, the need to calibrate most systems necessitating fingerpricks, skin reactions, and costs and poor reimbursement. In a recent Swedish cost-effectiveness analysis the Minimed 670G HCL system was associated with a quality-adjusted life-year (QALY) gain of 1.90 but higher overall costs *versus* CSII, leading to an incremental cost-effectiveness ratio (ICER) of SEK 164,236 per QALY gained (€15,500 or US$17,250). The authors concluded that at a willingness-to-pay threshold of SEK 300,000 per QALY gained (or €28,000 or US$31,500), this HCL system likely represents a cost-effective treatment option for people with T1DM in Sweden.[68]

Other barriers include a subject's level of numeracy and literacy, difficulties in carb counting, uncertainty on how to best interpret and use the data to make clinical decisions, development of alarm fatigue, time constraints in some diabetes clinics, information overload for some, and lack of systematic approach to data interpretation.

Even when all these novel systems may reduce burden (reduced fear of hypoglycemia, fewer alarms, self-learning algorithms in HCL systems), diabetes management still places a high burden on the individual with diabetes.

Conclusion

The introduction of isCGM and RT-CGM has transformed diabetes care. SAP therapy and HCL systems are at a stage where they can really make a difference in the daily life of our people with diabetes by reducing time in hypoglycemia, increasing time in range, decreasing glycemic variability, and improving long-term glucose control. The success of these novel technologies is however critically dependent on the level to which people are educated, capable, and motivated to use them. Successful implementation of these novel technologies might mean the end of severe acute and chronic invalidating complications.

Author's Note

CDB conceived the idea for the manuscript and decided the overall theme and content. CDB and FDR drafted the manuscript. All authors critically reviewed and approved the final submission.

Conflict of interest statement

CDB is a consultant for Abbott, A. Menarini Diagnostics, Lilly, Medtronic, Novo Nordisk, and Roche Diagnostics. The other authors have no conflicts of interest to declare.

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