Nutrition, Metabolism & Cardiovascular Diseases (2019) **29**, 421–431

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

VIEWPOINT

The use of real time continuous glucose monitoring or flash glucose monitoring in the management of diabetes: A consensus view of Italian diabetes experts using the Delphi method

D. Bruttomesso [a], L. Laviola [b], A. Avogaro [a], E. Bonora [c], S. Del Prato [d], S. Frontoni [e], E. Orsi [f], I. Rabbone [g], G. Sesti [h], F. Purrello [i,*] on behalf of the Italian Diabetes Society (SID)

[a] *Division of Metabolic Diseases, Department of Medicine, University of Padova, Padova, Italy*
[b] *Department of Emergency and Organ Transplantation, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari Aldo Moro, Bari, Italy*
[c] *Division of Endocrinology, Diabetes and Metabolism, University and Hospital Trust of Verona, Verona, Italy*
[d] *Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*
[e] *Endocrinology and Metabolism Fatebenefratelli Hospital, Dept. of Systems Medicine, University of Rome Tor Vergata, Rome, Italy*
[f] *Diabetes Unit, Fondazione IRCCS 'Cà Granda - Ospedale Maggiore Policlinico', Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy*
[g] *Department of Paediatrics, University of Turin, 10126 Turin, Italy*
[h] *Department of Surgical and Medical Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy*
[i] *Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy*

Received 19 October 2018; received in revised form 16 January 2019; accepted 31 January 2019
Handling Editor: A. Giaccari
Available online 10 February 2019

KEYWORDS
Real time continuous glucose monitoring (rtCGM);
Intermittently viewed continuous glucose monitoring (iCGM);
Diabetes mellitus;
Delphy method

Abstract Until recently, in Italy, the use of continuous glucose monitoring (CGM) systems has been limited, but is now rapidly increasing, including the so-called real-time CGM (rtCGM) and the intermittently viewed CGM (iCGM), also called Flash Glucose Monitoring (FGM). These technologies overcome many of the limitations of self-monitoring of blood glucose (SMBG) by fingerprick and allow to go beyond HbA1c to check glucose control in diabetes. However, standardized protocols for applying and interpreting rtCGM and FGM data are lacking. In this paper, we delineate a consensus amongst Italian diabetes physicians on the attributes of rtCGM and FGM technologies, and introduce a consistent approach for their use by Italian healthcare professionals. Most experts consider rtCGM and FGM as two separate categories of interstitial subcutaneous fluid (ISF) sensing technologies, and see them as superior to SMBG. Furthermore, there is strong consensus that rtCGM and FGM reduce hypoglycemia risk, increase the amount of time in the target glucose range and augment treatment satisfaction. However, there is still no agreement on the indication of the FGM for subjects who suffer asymptomatic hypoglycemia. Consensus on the role of education in initiating and optimizing use of rtCGM/FGM and about the interpretation of glucose trends was near unanimous, whereas no consensus was reached on the statement that there are no disadvantages/risks of rtCGM/FGM. Some issues remain in rtCGM/FGM management: a) risk of excessive correction of high or low glucose; b) risk of alert fatigue leading to alert silencing or rtCGM termination; c) allergic reaction to the adhesive keeping rtCGM or FGM sensors in place. The panel almost unanimously agreed that sensor accuracy depends on multiple variables, that alarm setting should be individualized, and that global

* Corresponding author.
E-mail address: fpurrell@unict.it (F. Purrello).

https://doi.org/10.1016/j.numecd.2019.01.018

glycemic profile represent an useful tool in interpreting glucose data. More clinical studies and a wider use of these devices will increase the efficacy and effectiveness of continuous glucose monitoring in Italy.

Introduction

Most people with diabetes in Italy monitor their glucose using SMBG. However, SMBG by intermittent capillary sampling gives just snapshots of BG concentration. Moreover, due to pain and inconvenience, many patients may not perform frequent SMBG [1,2] when it is needed.

The availability of continuous glucose monitoring (CGM), through sensors inserted subcutaneously to measure glucose levels in the interstitial fluid, addresses both issues by reducing patients' discomfort and providing vastly more glucose data [3]. Two types of continuous glucose monitoring (CGM) systems are currently available: real-time CGM (rtCGM) and intermittently viewed CGM (iCGM), also called Flash Glucose Monitoring (FGM). To maintain clear distinction throughout this article we will refer to these technologies as rtCGM and FGM.

Both systems provide information about current and previous glucose levels, as well as glucose trends and anticipated future glycemic status. However each technology has its own unique features, as shown in Table 1 and as discussed in a 2017 international consensus on the use of CGM [4]. Both rtCGM and FGM sensors collect real-time glucose readings continuously. FGM provides this information each time the user actively scans the sensor with the device reader or via an app on their smartphone, whereas rtCGM passively transmits this information without user engagement. Furthermore, rtCGM alerts users of low and high glucose, whereas FGM does not. In addition, FGM is itself a blood glucose meter, making capillary blood glucose measurement much more convenient when needed.

In Italy the most used rtCGM systems are the Dexcom G5 (Dexcom, Inc.) and Medtronic Enlite (Medtronic, Inc.), both using a transcutaneous sensor. Recently, the Eversense (Senseonics, Inc.) rtCGM has been introduced, that uses the first implantable subcutaneous sensor. At the time of writing, only one FGM system was available, the Freestyle Libre system (Abbott Diabetes Care).

Table 1 Distinct features of real time CGM and FGM systems.

Feature	rtCGM	FGM
Glucose sensing	ISF	ISF
Calibration	Once or twice daily with SMBG (Dexcom G6 can be calibrated with a scan code)	Factory calibrated
Fingerprick SMBG test required	To calibrate and for insulin dosing (Dexcom G5 and G6 don't require SMBG test for insulin dosing). If glucose alerts and readings do not match symptoms or expectations, or if no trend arrow is displayed (Dexcom G5, G6)	To confirm sensor reported hypoglycemia or impending hypoglycemia; at times of rapidly changing glucose; if symptoms don't match reading.
Interference from acetaminophen	Yes with Dexcom G4/G5 Yes with Medtronic Enlite No with Dexcom G6 No with Eversense	No
Duration of sensor life	6 days (Enlite); 7 days (DexcomG5), 10 days (Dexcom G6); 6 months (Eversense)	14 days (in EU) 10 days (in US)
Data update cycle	Every 5 min automatically	When sensor is scanned with the reader or smartphone app
Immediate access to glucose values	Button push	By scanning
Insulin dosing without confirmatory fingerstick testing	No (Enlite and Eversense) Yes (Dexcom G5, G6)[c,d]	Yes (in EU)[a] Yes (in US)[b]
Recommended Sensor site	Abdomen (transcutaneous), upper arm (implantable)	Back of upper arm
High/low glucose alerts	Yes	No
Connection with CSII pumps	Yes	No

FGM, flash glucose monitoring; rtCGM, real-time continuous glucose monitoring; ISF, interstitial fluid; CSII. Continuous subcutaneous insulin infusion.

[a] Manufacturers guidance, www.freestylediabetes.co.uk/images/uploads/documents/FreeStyle_Libre_Manual.pdf, accessed November 2018.
[b] Manufacturers guidance, www.myfreestyle.com/provider/sites/all/themes/provider20/pdf/FreeStyle-Libre-In-Service-Guide.pdf.
[c] Manufacturers guidance: www.dexcom.com/fingersticks, accessed November 2018.
[d] Manufacturers guidance https://s3-us-west-2.amazonaws.com/dexcompdf/G6-CGM-Users-Guide.pdf? accessed November 2018.

Several studies have shown that both rtCGM and FGM have a positive effect on metabolic control [5–9], and on the quality of life. However, the available evidence does not cover exhaustively issues such as the perception of differences between rtCGM/FGM vs SMBG, the use of glucose values and trends to guide therapeutic decisions, the ideal patient profile and the impact on everyday life.

In Italy, the use of glucose sensing technologies is rapidly increasing, thus we intend here to establish a consensus on the features of rtCGM and FGM, and to validate a consistent approach to their use in clinical diabetes care.

We used PubMed to survey the available literature for evidence about rtCGM or FGM efficacy, accuracy, safety, patient satisfaction and quality of life, compared either to SMBG or other standard of care. Published randomized clinical trials and observational studies (either cross-sectional or prospective/retrospective) meta-analyses and reviews were considered. Although not being strictly systematic, we are reasonably sure to have considered all relevant papers, although we cannot exclude that some may have escaped our notice. The summarized results of this search are presented in the *Survey of published evidence* below. This knowledge base was used to develop the scope and content of the Delphi survey questionnaire ultimately submitted to the expert panel for consensus. It was devised in the form of 59 Likert statements that probed agreement or disagreement against a selection of points on the appropriate use of rtCGM or FGM as diagnostic or therapeutic devices in the management of people with diabetes.

The implantable rtCGM sensor Eversense was not included in the survey, due to limited published literature and clinical experience. Similarly, there is no mention of CGM in pregnant women, due to limited experience in this context. In addition, the main focus of both the review and the survey was on the use of rtCGM or FGM systems in subjects on multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII), but not using sensor-augmented pump therapy (SAP).

Survey of published evidence

The impact of rtCGM and FGM on glycemic control in diabetes

Several RCTs have shown that rtCGM and FGM improve a range of outcomes in patients with type 1 or type 2 diabetes. Change in HbA1c is the most notable glycemic indicator in current clinical practice, but other important indicators are the time spent within the target glucose range or in hypoglycemia, glycemic variability and treatment satisfaction.

Change in HbA1c

Several studies (JDRF, DIAMOND, GOLD, SWITCH) have shown that the use of rtCGM in adults and children with type 1 diabetes reduces HbA1c levels (from 0.4 to 1.0%) [10–13], irrespective of the insulin delivery method [5].

To date FGM has been tested in 2 RCTs (IMPACT [14] and REPLACE [15]) in adults with type 1 or insulin-treated type 2 diabetes. Neither study found significant differences in HbA1c using FGM or SMBG. On the other side, a single-arm prospective trial in children and teenagers with type 1 diabetes (SELFY) and a recent observational, real world analysis on adult patients with type 1 diabetes found a positive effect of FGM on HbA1c levels [16,17].

Time in target

The time with glucose levels within a target range influences both HbA1c and glycemic variability. For the purposes of clinical studies, a target glucose range of 3·9–10·0 mmol/L (70–180 mg/dL) is typically specified. The use of rtCGM in patients with type I diabetes increases significantly the time in target. The JRDF CGM, DIAMOND, SWITCH, IN CONTROL and REPLACE-BG studies all reported increases of 1.3–2.3 h/day [10,11,13,18,19].

Regarding FGM the IMPACT and SELFY studies found a significant increase of the time on target (0.9–1.0 h/day) both in adults and children/teenagers [14,16]. On the other side the REPLACE study [15] on FGM in adults with insulin-treated type 2 diabetes found no significant effect on the time in target.

Risk of hypoglycemia

Reducing the risk of hypoglycemia is a core objective for managing people with diabetes, especially those on insulin or on sulphonylureas. FGM and rtCGM both make a big difference in this outcome. In the IMPACT and REPLACE studies [14,15], the time that users of the FreeStyle Libre FGM system spent below 3.9 mmol/L (70 mg/dL) was reduced by 38% (IMPACT) and 43% (REPLACE), compared to subjects using SMBG. Nocturnal hypoglycemia was also reduced, by 40% in IMPACT [14], by 52% in REPLACE [15]. Similar results, using the Dexcom G4 Platinum rtCGM system, were demonstrated in the DIAMOND and GOLD studies [11,12].

CGM and FGM in individuals at high risk of hypoglycemia

The use of rtCGM has a huge impact on individuals with type 1 diabetes prone to severe hypoglycemia. The impact of rtCGM has been tested in the HypoDE study [20] on patients with impaired hypoglycaemia awareness or severe hypoglycaemia treated with MDI, and in the IN CONTROL study [18] on patients with impaired hypoglycaemia awareness. In HypoDE study rtCGM decreased the number of hypoglycemic events by 72% with respect to SMBG, and nocturnal hypoglycemia was reduced by 65% [10]. Similar results were seen in the IN CONTROL study [18].

Sensor calibration, accuracy and wear life

Both rtCGM and FGM measure glucose in ISF rather than in capillary blood as measured by SMBG meters. In this context, it must be understood that blood and ISF are different physiological compartments that follow different

dynamics [21]. This has several important consequences for interpretation of rtCGM and FGM data. First, there is a time-lag between blood and ISF readings as glucose takes time to equilibrate between the two compartments. Under steady state conditions this is estimated to be 5–10 min for rtCGM [22] and FGM [23]. Secondly, the accuracy of the sensor ISF glucose measurements is not constant, and will vary depending on the blood glucose concentration and the rate of blood glucose change [24,25]. In a head-to-head comparison of the accuracy of FreeStyle Libre and Dexcom G 5 it was recently shown that both systems perform safely and efficiently but the DG5M sensor has greater accuracy across all glucose values except in hypoglycaemia. Considering accuracy during blood glucose swings, Dexcom G5 performed better than the FSL when glucose increased, both slowly and rapidly. No differences in accuracy were observed when glucose levels decreased rapidly [26].

It will be interesting comparing G6 and new format of Libre. There is no standard metric for quantifying the accuracy of rtCGM or FGM sensors, and it is important to understand the real-world conditions that influence accuracy in order to ensure that treatment decisions based on ISF sensor data are both effective and safe [27].

Most currently available rtCGM sensors have a 5–7 day wear life, whereas the FreeStyle Libre FGM sensor has a 14-day wear life (Table 1). More recently, the Eversense implanted sensor has demonstrated a 180-day life [28], and the Dexcom G6 rtCGM with a 10-day wear life has recently become available [29].

An important difference between rtCGM and FGM systems is that, to maintain accuracy, rtCGM require the user to perform once or twice-daily sensor calibration using a SMBG test (see Table 1). The possible exception is the Dexcom G6 that allows users to scan a calibration code at start up, with optional SMBG calibration if the code is lost. The efficacy of this process will become clear as users build experience with the G6. In contrast, FGM sensors are factory calibrated. Another notable difference between rtCGM and FGM sensor technologies is that FGM sensors operate at a much lower electrical potential than rtCGM sensors [30], which improves their stability.

Trend arrows and insulin dosing decisions

An important advantage of rtCGM and FGM devices is that they typically provide directional trend arrows alongside the current glucose reading. Trend arrows provide information on the direction and the rate of change (RoC) of ISF glucose levels and are generated from the slope of ISF glucose values over the previous 15 min. The pairing of a current glucose reading with a directional trend arrow is a powerful tool to assist with making diabetes self-management decisions, not possible with SMBG testing.

One treatment area that still requires SMBG is that of insulin dosing. The majority of rtCGM systems are not approved for users to make insulin dosing decisions without the need for an SMBG test to confirm blood-glucose levels. However, at the time of writing 3 systems are approved for insulin dosing without the need for an adjunct SMBG test (both in the EU and the US): the factory-calibrated FreeStyle Libre FGM system and the Dexcom G5 and G6 rtCGM systems (see Table 1). At present, for other systems with a similar or lower level of accuracy it is required that SMBG measurements should be performed to confirm rtCGM readings prior to making insulin management decisions aimed at addressing acute changes in glucose levels.

The utility of trend arrows for insulin dosing is a topic of intense discussion. Recent surveys indicate that people with diabetes using rtCGM rely on trend arrows to calculate mealtime insulin boluses and also to make corrective insulin dose adjustments between meals [31]. Importantly, in response to RoC trend arrows, respondents using rtCGM made significantly larger dose adjustments than would be recommended by published algorithms for using RoC trend arrows for insulin dose management [32,33].

Previously, subjects in clinical trials using rtCGM have been provided with treatment algorithms for managing insulin dosing decisions in line with trend arrows data [10,34], and a range of real-world methods have been proposed for adjusting insulin doses using trend arrows. Methods proposed by Scheiner [35], Pettus/Edelman [36] and Aleppo (specific to Dexcom G5) [37] rely on using trend arrows to anticipate a future glucose value to recommend an adjustment in insulin dose. Users can then use their own predetermined insulin sensitivity factor to add or subtract insulin, based on insulin sensitivity. Recently ways to adjust insulin dosing have been proposed also for the FreeStyle Libre [38].

To avoid potentially confusing mathematical calculations to manage insulin dosing decisions, two groups have proposed trend arrow adjustment tools (TAATs), in which each trend arrow orientation is associated with a fixed, pre-calculated dose-change to the regular mealtime insulin bolus. The first of these was developed by Heffernan and colleagues for children on CSII therapy, and directed them to add or subtract either 0.5 or 1.0 unit of mealtime insulin depending on the trend arrow orientation [39]. This TAAT was effective in a pool of 20 children and adolescents. Similarly, Klonoff and Kerr have proposed a TAAT for insulin-treated adults [40], directing a fixed 1.0, 1.5 or 2.0 unit insulin adjustment depending on the direction and rate of change shown by the trend arrows. Both TAATs assume a standardized insulin sensitivity factor, and that the rate and direction of change in glucose for each trend arrow will be consistent for around 45 min following a pre-meal reading.

Retrospective analysis and reporting

In addition to the immediate information provided by the current glucose reading and the associated trend arrows, an acknowledged benefit of rtCGM and FGM systems is that they can store glucose readings for retrospective analysis of glycemic control over weeks or months, depending on the period over which a user has worn a sensor. Real time CGM and FGM systems both automatically collect and save real-time glucose measurements, however for FGM the user

must physically scan the sensor with a reader or smartphone at least once every 8 h to ensure optimal data collection, whereas rtCGM systems automatically transmit the data to the reader or smartphone.

Real time CGM and FGM systems each have device-specific reporting tools that can provide data on collections of time-stamped glucose readings and trends over a single day, or many days. An important development for retrospective analysis of rtCGM/FGM profiles has been the introduction of the ambulatory glucose profile (AGP), which is an internationally agreed standard for summarizing and interpreting daily glycemic patterns using large amounts of data collected from rtCGM or FGM systems [41,42].

The AGP displays large amounts of glucose data as if all the readings had occurred in a single 24-h period - the so-called 'modal' day. A profile can be created from as little as 5 days of such data or from as much as 3-months. Such 'global' profiles can provide important feedback on hypoglycemia, especially nocturnal patterns of low glucose, as well as periods of glucose variability, including post-prandial peaks. The impact of insulin doses, meals, exercise, stress and other variables can also be assessed using profiles that cover single days or more-extended periods to examine the longer-term outcomes of treatment changes. A limitation of the AGP and other modal reports is that they work best if patients use their rtCGM/FGM devices to log daily actions such as insulin doses, meals, snacks, exercise, work, and sleep.

Patient satisfaction with rtCGM and FGM

Insulin therapy requires that frequent glucose monitoring is part of achieving tight glycemic control. However, for many people with diabetes, poor engagement with SMBG can be a barrier to optimal glucose control [43]. Patient reported outcomes during clinical studies using rtCGM indicate improved diabetes treatment satisfaction and overall sense of well-being [12]. Significantly, fear of hypoglycemia is reduced by rtCGM [12]. rtCGM Satisfaction Scale scores for subjects in clinical studies also indicate a positive impact on both treatment benefits and quality of life indices [11]. For FGM, in each of the IMPACT, REPLACE and SELFY studies [14–16] the intervention group indicated a positive impact of FGM compared to SMBG in terms of use of the system, improved diabetes treatment satisfaction scores, and diminished anxiety for children or adults with type 1 or type 2 diabetes.

Patient education

In real-world settings many rtCGM or FGM users may struggle to sustain prolonged use because of various concerns over: accuracy; device education; frequency of alerts and; interruptions to daily life. A qualitative meta-analysis of available studies on how people with type 1 diabetes live on a daily basis with rtCGM indicate that, alongside the acknowledged healthcare benefits, there are a range of physical, emotional and social issues that must be managed by rtCGM users [44]. There is therefore a considerable need to ensure that implementing rtCGM or FGM for people with diabetes is accompanied by education and support measures that improve the ability of the user, both to optimize their use of the technology and to set their expectations in line with long-term use of rtCGM or FGM. These should include the elements listed in Table 2.

Methods

Study design

Delphi method

To reach a consensus, a modified Delphi method was used. Delphi is a structured method that can be used to obtain consensus among medical experts to develop clinical guidelines, standards of care or clinical indicators [45,46]. The expert participants freely, individually and anonymously provide their opinion, through one or more rounds of discussion. The process usually concludes when an agreement on the discussed topic has been achieved. In this study, each expert expressed their level of agreement according to the following 5-point Likert scale: 1 = absolutely disagree, 2 = disagree, 3 = agree, 4 = more than agree, 5 = absolutely agree. We considered a positive consensus was reached when the sum of items 1 and 2 (Disagree) or 3, 4 and 5 (Agree) reached 66%. No consensus was reached when the sum of the responses for a negative consensus (1 and 2) or a positive consensus (3, 4 and 5) was <66%.

Development and validation of the Delphi questionnaire

The Delphi method was applied in a 4-stage process. (1) Literature research was undertaken covering the application and utility of rtCGM and FGM in the management of

Table 2 Minimum requirement for education and support to effectively use of rtCGM and FGM systems.

1. Initial education on technical aspects of sensor application, sensor reading and data entry.
2. Understanding the use of ancillary devices, such as smartphones and tablets, internet, desktop or laptop computers, apps and other software.
3. Understanding that ISF and blood glucose are measured differently, and the need to account for the sensor lag periods during steady state and at times of rapid change in glucose levels.
4. Education on real-time decision-making in response to glucose readings and associated trend arrows, including how to make therapeutic adjustments in response to rising or falling glucose readings, and guidance on how to make insulin-dosing decisions based on rtCGM/FGM data.
5. Education on all factors that might impact glucose readings each day and between days, including: type and quantity of food and drink; physical activity; insulin and other medications; stress or sickness.
6. For rtCGM systems, clear instruction on: how to effectively calibrate the sensor and setting alerts and alert management, in consultation with their HCP.

FGM, flash glucose monitoring; rtCGM, continuous glucose monitoring; ISF, interstitial fluid; HCP, healthcare professional.

Table 3 Topic areas selected and validated for inclusion in the Delphi questionnaire.

1. Clinical/therapeutic perception of FGM and rtCGM in comparison with SBMG
2. Use of FGM/rtCGM or SMBG for therapeutic decisions and management
3. Calibration procedures
4. Sensor accuracy
5. Patient profile for rtCGM/FGM usage
6. Educational programs for clinicians and patients
7. Trend arrows interpretation
8. Information provided by rtCGM and FGM and data analysis
9. Disadvantages, risks and contraindications of FGM and rtCGM
10. Alerts setting

FGM, flash glucose monitoring; rtCGM, real time continuous glucose monitoring; SMBG, self-monitoring of blood glucose.

type 1 or insulin treated type 2 diabetes (see above). Based on this research, a questionnaire was developed that contained a list of items and statements aimed to test the attitude and opinion of Italian clinicians on the appropriate use of rtCGM or FGM as diagnostic/therapeutic devices in the management of people with diabetes. (2) These statements were reviewed by an advisory board of 10 Italian experts in diabetes (the authors of this paper). After discussion, the advisory board rephrased and modified the questionnaire, obtaining 17 final items, each detailed in 1 or more statements, as specified in the results section. (3) The questionnaire was then submitted to 14 external validators. Following validators comments, 16 items were defined according to the topic areas listed in Table 3. (4) The finalized Delphi questionnaire (Tables 4a–c) was electronically delivered to 74 Italian diabetes specialists, expert in rtCGM and FGM, working in separate outpatient diabetes centers (58 adult and 16 pediatric).

Results and discussion

A consensus was reached against all but two of the items in the survey questionnaire, in that >66% of responses either indicated agreement with each statement by selection of items 3, 4 or 5 on the Likert scale, or indicated disagreement by selecting items 1 or 2. This level of consensus was achieved after a single round of polling. Although we did not reach consensus for two items (8.1 and 14.1) in the present study, we did not proceed for a second Delphi round because of limited information from

Table 4a Results of the Delphi method survey of 74 expert diabetes physicians from diabetes centres in Italy: question groups 1–8.

	Response (n=74)					Consensus score	
Survey question group	**1**	**2**	**3**	**4**	**5**	**Agree**	**Disagree**
1. rtCGM or FGM technologies							
1.1 Provide information on glycemic control, not achievable with SMBG.	0	2	3	16	53	97%	3%
1.2 Provide information (glycemic profile, rate of glucose changes and alerts) that might improve the efficacy of rtCGM or FGM, over SMBG.	1	2	1	24	46	96%	4%
1.3 Provide clinical benefits, thanks to real-time therapeutic decisions.	0	2	17	28	27	97%	3%
2. Patients using FGM have to measure capillary blood glucose levels in order to take a therapeutic decision if:							
2.1 Symptoms do not match with sensor glucose measurement.	1	3	5	17	48	95%	5%
2.2 Hypoglycemia needs to be confirmed	0	2	7	16	48	96%	3%
2.3 Glucose levels are rapidly changing	0	7	13	20	34	91%	9%
3. Patients using a rtCGM device not authorized as a substitute for SMBG, have to measure capillary glucose blood levels to:							
3.1 Determine the insulin dose	1	8	17	22	26	88%	12%
3.2 Confirm and treat hypoglycemia	1	3	17	19	34	95%	5%
3.3 Perform device calibration	3	5	5	8	53	89%	11%
4. Comparing rtCGM and FGM systems							
4.1 FGM has different features compared to rtCGM	0	4	14	21	35	95%	5%
4.2 FGM might be considered as a CGM on demand	4	11	27	16	16	80%	20%
4.3 FGM could be considered as a real time CGM	15	37	13	4	5	30%	70%
5. Calibration procedure							
5.1 It can be performed at every moment of the day	29	22	13	4	6	31%	69%
5.2 It doesn't bias glucose measurement	18	32	13	7	4	32%	68%
5.3 It might represent a limiting factor to patient's compliance	1	17	26	22	8	76%	24%
5.4 It might represent a limiting factor for patient's satisfaction	0	20	23	23	8	73%	27%
5.5 If factory calibrated (as for FGM), is more accurate, since it prevents patient's errors	0	19	25	25	5	74%	26%
6. Sensor accuracy							
6.1 It depends on glycemic levels and the rate of blood glucose changes	0	6	19	25	24	92%	8%
7. rtCGM or FGM, compared to SMBG							
7.1 Decrease glycated hemoglobin amounts	0	7	25	29	13	91%	9%
7.2 Increase the amount of time that glucose levels are within the target glycemic range	0	0	17	38	19	100%	0%
7.3 Reduce hypoglycemia risk	0	1	17	29	27	99%	1%
7.4 Increase treatment's satisfaction	0	0	12	38	24	100%	0%
7.5 Have a benefit directly proportional to the frequency of use	0	0	2	21	51	100%	0%
8. rtCGM or FGM							
8.1 FGM is suitable for type 1 diabetes patients, with asymptomatic hypoglycemia	15	18	16	11	14	55%	45%
8.2 rtCGM is suitable for type 1 diabetes patients, with asymptomatic hypoglycemia	0	0	3	22	49	100%	0%
8.3 rtCGM and FGM are suitable for type 1 diabetes patients with unsatisfactory metabolic control	0	2	18	24	30	97%	3%
8.4 rtCGM and FGM are beneficial for both type 1 or type 2 diabetes patients using either MDI or CSII	0	3	13	29	29	96%	4%

Table 4b Results of the Delphi method survey of 74 expert diabetes physicians from diabetes centres in Italy: question groups 9–13.

	Response (n=74)					Consensus score	
Survey question group	**1**	**2**	**3**	**4**	**5**	**Agree**	**Disagree**
9. Regarding the education for the use of rtCGM/FGM							
9.1 Patient needs to be instructed on how to insert/remove the sensor, to use the transmitter and receiver and ancillary devices (smartphones, internet, computer, software)	0	0	3	14	57	100%	0%
9.2 Patient needs to be instructed on how to interpret sensor measurements and to take appropriate actions	0	0	4	5	65	100%	0%
9.3 Patient needs to be trained on how to respond to real-time information, received by the sensor	0	0	3	6	65	100%	0%
9.4 Patients needs to accurately specify food, physical activity, insulin/medications and other events that might cause a change in blood glucose levels. It is important to contextualize rtCGM and FGM data	0	2	9	10	53	97%	3%
9.5 Efficacy depends on the ability of the patient to properly use sensor measurements	0	0	4	15	55	100%	0%
9.6 With a poor training, patients might take risky therapeutic adjustments	0	0	10	12	52	100%	0%
9.7 Diabetes healthcare provider community need to set up educational courses for an appropriate use of rtCGM and FGM devices	0	1	2	8	63	99%	1%
10. The therapeutic management through rtCGM/FGM needs to take into consideration that:							
10.1 With the same glucose level, insulin doses might widely vary, according to glycemic trend	0	0	14	31	29	100%	0%
10.2 In order to adjust real time insulin doses, patients needs to take into consideration trend arrows information (and alerts, if available)	0	0	5	27	42	100%	0%
10.3 When determining insulin dose, the patient needs to take into consideration the expected glucose value, based on the trend arrow, rather than the absolute glucose value	0	0	15	32	27	100%	0%
11. Regarding rtCGM/FGM trend arrows:							0%
11.1 It is mandatory to know differences among devices, on how trend arrows are displayed and defined	0	0	11	23	40	100%	0%
11.2 When using trend arrows, variables to take into consideration are: quality and amount of meal's composition, physical activity performed or to perform (intensity and length), medications increasing glucose levels, stress level and comorbidities	0	0	13	24	37	100%	0%
12. The glycemic profile analysis measured by rtCGM/FGM in the last 3-24 hours, provides information on:							
12.1 Efficacy of prandial/correctional bolus	0	1	13	27	33	99%	1%
12.2 Effectiveness of meals components	0	2	18	26	28	97%	3%
12.3 The presence of post-prandial peaks	0	2	18	24	30	97%	3%
12.4 Physical activity's effects	0	0	9	26	39	100%	0%
12.5 Stress impact	0	2	13	25	34	97%	3%
12.6 Night glycemic patterns	0	3	7	19	45	96%	4%
12.7 Basal insulin dose correctness	0	4	9	28	33	95%	5%
13. The retrospective analysis of rtCGM/FGM data needs to consider:							
13.1 Only global glycemic profiles	21	39	8	6	0	19%	81%
13.2 The analysis of global glycemic profiles, at first, and daily glycemic profiles, afterwards	0	0	10	33	31	100%	0%
13.3 A deep daily analysis is necessary especially when there is a wide glycemic variability, which makes difficult to identify	1	1	10	23	39	97%	3%

the literature to assess these items. We will examine in the discussion section the topics that did not achieved consensus. The Delphi method survey response data is provided in Table 4a–c and discussed below.

Clinical/therapeutic perception of FGM and rtCGM in comparison with SBMG

Perceptions of value for both rtCGM and FGM are high compared to SMBG. 97% of respondents agreed that both technologies are superior to SMBG (Table 4a, section 1). This sense of value is founded in the ability of both rtCGM and FGM to provide information on glycemic profiles and rate of glucose change not achievable with SMBG (96% consensus). There was strong consensus (97%) that these features can provide clinical benefits, as they would enable users to make real-time therapeutic decisions. In addition, there was clear consensus in the expert panel on specific circumstances that require fingerprick SMBG testing in both rtCGM and FGM users (Table 4a, sections 2 and 3).

However, rtCGM and FGM are distinct technologies with different distinguishing features. rtCGM sensors

Table 4c Results of the Delphi method survey of 74 expert diabetes physicians from diabetes centres in Italy: question groups 14–16.

	Response (n=74)					Consensus score	
Survey question group	**1**	**2**	**3**	**4**	**5**	**Agree**	**Disagree**
14. Regarding disadvantages and risks of rtCGM/FGM, I believe that:							
14.1 There is no disadvantage/risk	6	40	15	9	4	38%	62%
14.2 There is an excess of hypo- and hyperglycemia correction	0	9	26	20	19	88%	12%
14.3 Patient might silence rtCGM alerts or underuse the device, as a consequence of the alerts	0	5	24	29	16	93%	7%
14.4 There is an allergic reactions and irritation from the adhesive	0	7	26	25	16	91%	9%
15. rtCGM/FGM are contraindicated:							
15.1 In patients not considered able to manage the device	0	4	11	9	50	95%	5%
16. Regarding alerts settings, I believe that:							
16.1 Hypo- and hyperglycemia levels do not represent the target glycemic range of the patient	0	6	30	18	20	92%	8%
16.2 Hypo- and hyperglycemia level alert settings are equal among patients	40	30	2	2	0	5%	95%
16.3 Hypo- and hyperglycemia level alert settings depend on the degree of patient's glycemic control	0	1	24	36	13	99%	1%
16.4 It is recommended to set the hypoglycemia alert of 10-20 mg/ml, higher than the real patient's threshold	3	12	32	20	7	80%	20%
16.5 It might be useful to set alerts with diverse thresholds for Hypo- and hyperglycemia, at different times of the day.	0	5	25	30	14	93%	7%

require once- or twice-daily calibration using an SMBG test, whereas FGM sensors are factory calibrated. The majority of rtCGM systems are not approved for users to make insulin dosing decisions without the need for an SMBG test to confirm blood-glucose levels. FGM using the FreeStyle Libre system is approved in the US and in the EU for insulin dosing without the need for an adjunct finger-prick blood test, as are the Dexcom G5 and G6 rtCGM systems (see Table 1).

An important consequence of these distinctions is confirmed by the expert panel in section 4 of the survey. There was consensus that FGM is distinct from rtCGM (95%) and cannot be considered as an rtCGM system (70%). However, even though it is continually sensing, FGM was considered to be an 'intermittent' CGM or a CGM 'on demand' (80%), since it must be scanned to acquire this data. Thus, there is clear differentiation in the opinion of the expert panel between rtCGM and FGM as separate categories of ISF sensing technologies.

Features not considered here and possibly important in choosing the system better tailored for individual patients include minimum age for use, indication for use in pregnancy, real-time remote monitoring (data sharig) [47].

Use of rtCGM/FGM versus SMBG for therapeutic decisions and diabetes management

The evidence base supporting improved glycemic control for users of rtCGM and FGM technologies is fully appreciated by the expert diabetes physicians in this Italian survey (Table 4a, Section 7). There was very strong consensus, both that rtCGM and FGM will reduce hypoglycemia risk for users (99%) and also increase the amount of time in the target glucose range (100%). This confidence is important given that minimizing hypoglycemia is a major part of clinical practice. Consensus that rtCGM and FGM can both reduce HbA1c as part of care compared to SMBG was also high (91%), even though the available RCT data confirms this outcome for rtCGM rather than FGM, which achieved this only in children and teenagers with type 1 diabetes in a single arm, prospective trial [16]. The overall confidence in these systems is reflected in the 100% agreement that rtCGM and FGM will increase treatment satisfaction among patients, which is again in line with the patient-reported outcomes from RCTs.

Sensor calibration and accuracy

The need to use SMBG to calibrate rtCGM systems means that strip use will be higher for rtCGM users, whereas FGM is calibrated in the factory and the user does not need to perform this task. This need for user calibration is a key difference between rtCGM and FGM. Infrequent or incorrect calibration by patients using SMBG can potentially reduce the accuracy of rtCGM, an issue that does not affect FGM systems. These important aspects of rtCGM and FGM were appreciated by the diabetes experts in the survey, who showed strong consensus with these distinctions (Table 4a, sections 3.1–3.3, 5.2, 5.5), and there was agreement that this could also limit patient satisfaction and compliance with rtCGM systems (sections 5.3, 5.4, 73% and 76% consensus, respectively).

Perceptions of sensor accuracy of both rtCGM and FGM technologies was probed directly as part of the questionnaire (Table 4a, section 6), and there was clear understanding and agreement (92%) that accuracy depends on a range of variables, notably the glucose level and the rate of blood glucose change [24,25]. This is an important consideration. Since they measure glucose in ISF rather than in the blood, there is no standard metric for quantifying the accuracy of rtCGM or FGM sensors, and it is important to understand the real-world conditions that influence accuracy in order to ensure that treatment decisions based on ISF sensor data are both effective and safe [27].

Patient profile for rtCGM/FGM use

In terms of the type of patients for whom rtCGM or FGM are suitable technologies, our survey clearly showed high confidence in CGM as an effective system for improving glycemic control in people with type 1 diabetes on MDI or CSII, including those with asymptomatic hypoglycemia (Table 4a, section 8). There was consensus that FGM was effective in improving control in type 1 diabetes treated with MDI or CSII. However, there was not agreement on the indication of the FGM for subjects who suffer asymptomatic hypoglycemia (Table 4a, question 8.1). This is interesting, given the general notion that the absence of alarms is one of the key differences between rtCGM and FGM systems (Table 1). It is possible that the ever wider use of FGM in clinical practice may render physicians more confident on the global improvement of disease control, including reduction of hyoglycemia risk.

Equally important to note is the 95% consensus that rtCGM and FGM are both contraindicated in patients not able to manage these systems (Table 4c, section 15). This is a clear acknowledgement of the need for good engagement with the different capabilities of the technology, as outlined in several sections of the survey.

The need for education to support use of rtCGM/FGM

Consensus on the role of education in initiating and optimizing use of rtCGM/FGM amongst patients was near unanimous. Each aspect of the training needs of patients, as detailed in Table 2 was supported by 97%–100% agreement (Table 4b, Sections 9). This consensus indicates a central role for education that allows patients and healthcare professionals to integrate rtCGM/FGM into daily life with diabetes, and to make effective therapeutic decisions. This is underlined by the fact that 100% of respondents agreed that poor training might lead to patients making risky therapeutic adjustments (Table 4b, section 9.6). Similarly, it was recognized that the responsibility for providing education on rtCGM/FGM lies with the healthcare provider community (Table 4b, section 9.7).

Interpretation of trend arrows

Two sections of the Delphi questionnaire probed the expert panel on the issue of the application and utility of trend arrows in glycemic management for rtCGM/FGM users (Table 4b, sections 10, 11). Trend arrows add context to each glucose reading such that different therapeutic decisions may follow a reading at the same absolute glucose level. This concept of 'anticipated' glucose based on upward or downward trends is a key benefit for rtCGM/FGM and has a critical impact on insulin dosing decisions (Table 4b, section 10), as evidenced by the recent publications on how best to interpret trend arrow information in calculating safe and effective mealtime insulin and correction doses [35–40]. The integration of trend arrows into daily decisions requires both an understanding of how the glucose trend information is displayed for each device, and the rate of change it implies, as well as how different activities impact on glucose trends and rates of change (Table 4b, section 11). For each question in sections 10 and 11 there was a 100% consensus, stressing the importance of this aspect of rtCGM and FGM systems, and supported by the clear consensus for education in these aspects of rtCGM/FGM (Table 4b, section 9).

Information provided by rtCGM and FGM and data analysis

Glycemic data collected by rtCGM and FGM systems is acknowledged to have high impact for daily glycemic control. There was clear consensus that rtCGM/FGM can provide feedback on activities that affect glycemic control within 3 h, and also create 24-h profiles that reflect the impact of prandial/correction doses of rapid-acting insulin, as well as basal dose adjustments (Table 4b, sections 12.1, 12.7). Glycemic variability after meals (sections 12.2, 12.3) and overnight (section 12.6) are agreed to be notable capabilities of rtCGM/FGM, as well as the effects of physical activity and stress (sections 12.4, 12.5).

The responses focused on retrospective glycemic analysis using rtCGM/FGM were insightful. There was good consensus (81%) that extended global glycemic profiles, such as using AGP, should not be used as the only tools for retrospective analysis (Table 4b, section 13.1). Rather, there was 100% agreement that global profiles are a good place to start but must be followed by assessment of daily glycemic profiles in order to get as complete a picture of as many aspects of glucose control as possible (Table 4b, section 13.2). This is most emphasized when glycemic profiles highlight wide glycemic variability, which makes it hard to identify specific patterns and potential causes (Table 4b, section 13.3). This reflects the growing international consensus on the place of global profiling tools such as AGP in clinical practice [42,48,49].

Disadvantages, risks and contraindications of rtCGM and FGM

The acknowledged benefits of rtCGM and FGM technologies are accompanied by risks and disadvantages that must be considered before they can be fully adopted. This is reflected in section 14 of the Delphi survey. No consensus was reached among the expert group against the general statement that there are no disadvantages/risks of rtCGM/FGM (Table 4c, section 14.1). That 38% of respondents agreed with this statement is somewhat surprising, given the general notion that every device which may impact glucose monitoring and insulin therapy can have some notes of caution, disadvantages and even contraindications. It is possible that, for some of the diabetes experts who were surveyed, the accurate selection of patients to be provided with glucose sensors can in fact prevent most of the hypothetical disadvantages. In addition, it is possible that more direct clinical experience may be necessary to develop a full consensus on the balance between strengths and weaknesses.

As regards specific disadvantages/risks, there was strong consensus that three aspects of rtCGM/FGM could be problematic: These were that: a) there is a risk of excessive correction of high or low glucose (section 14.2); b) the benefits of rtCGM alerts would be counterbalanced if users developed so-called 'alert fatigue' and either silence the alert function or disengage from using rtCGM as a consequence (section 14.3); c) and that the adhesive necessary to keep rtCGM or FGM sensors in place on the skin can cause an allergic reaction (section 14.4). Each of these is an acknowledged burden of living with rtCGM and FGM and each must be addressed in education and training at the point of initiating rtCGM and FGM with new users.

Alert settings

High and low-glucose alerts are another important differentiating feature for rtCGM, as FGM systems do not have this capability. These were investigated further in Section 16. There was expert agreement that the alert settings in rtCGM should be set to match the individual glycemic needs of each patient, rather than use a standard setting for all rtCGM users (section 16.2, 16.3). This consensus also acknowledged that some patients might need different low and high glucose alert settings at different times of day (section 16.5). In an additional note of caution, there was 80% agreement that low-glucose alerts should be set at 10–20 mg/ml higher than the lower limit of the target glycemic range for rtCGM users (section 16.5), to further avoid adverse hypoglycemia.

The availability of predictive alarms for the implantable rtCGM Eversense may potentially improve diabetes management and prevent excessive glucose variations. However, there is no published literature to date and limited clinical experience on this feature.

Conclusions

Technologies aiming at measuring interstitial glucose concentrations have started a new era in the management of people with diabetes, providing diabetes teams and patients with glucose data and profile interpretation tools

which can improve metabolic control, optimize therapy management and foster disease awareness and optimal life choices in patients. In the first part of this paper we have summarized the published evidence on the benefits of FGM and rtCGM in people with diabetes. We have considered available meta-analyses, reviews and original papers. Literature search, however was not strictly systematic, so some data might be missing. In the second part, the results of the Delphi approach suggest that the diabetes professional community in Italy has gained considerable and uniform experience in clinical use of rtCGM and FGM. There is clear perception of the superiority of both rtCGM and FGM over SMBG, specifically for the advantages in term of hypoglycemia reduction and improvement in time in the target glucose range and treatment satisfaction. The panel acknowledged the distinct features of FGM and rtCGM: FGM sensors do not require calibration from the patient, are allowed for non-adjunctive use in insulin dosing and show no interference with acetaminophen, but are not indicated in subjects with hypoglycaemia unawareness. On the other hand, rtCGM devices are provided with alarms, can be connected with insulin pumps and store glucose values independently of user scanning, but most of them require periodic calibration and SMBG confirmation for insulin dosing. There is also clear understanding of the limitations in rtCGM/FGM management, including risk of excessive correction of abnormal glucose values, risk of alert fatigue leading to discontinuation, and potential skin allergic reaction. Unanimous consensus was reached on the essential role of education in initiating and optimizing use of rtCGM/FGM and in the interpretation of glucose trends. As technology provides more and more accurate and reliable tools, more clinical research projects and a wider use of these devices will increase the expertise of diabetes teams and ultimately improve everyday life in people with diabetes.

Conflicts of interest

DB has received speaker's fees and consultation fees from Abbott, Movi and Roche diagnostics.

LL has received speaker's fees and consultation fees from Abbott, Medtronic and Roche diagnostics.

AA, SF, IR, GS have nothing to disclose.

EB has received speaker consultation fees from Abbott and Johnson & Johnson and research grants from Menarini diagnostics and Roche diagnostics, outside the submitted work.

SDP reports grants from AstraZeneca, Boeheringer Ingelheim, Merk&Co, Novartis Pharmaceutical and personal fees from Abbott, AstraZeneca, Boeheringer Ingelheim, Eli Lilly & Co, GlaxoSmithKline, Merk & Co, Novartis Pharmaceuticals, Novo Nordisk, Sanofi, Servier, Takeda Pharmaceuticals, outside the submitted work.

EO has received consultation fees from Novo Nordisk and Eli Lilly.

FP reports grants from ABBOTT, SF, GS, IR niente, during the conduct of the study.

Author contribution

DB searched the literature, prepared the initial questionnaire and drafted the manuscript.

LL revised the initial questionnaire and drafted the manuscript.

AA, EB, SDP, SF, EO, IR, G S, FP, revised the initial questionnaire and contributed to the final version.

Funding

This study was supported by Abbott, Italy.

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