



Freestyle Libre trend arrows for the management of adults with insulin-treated diabetes: A practical approach

Cristina Bianchi ^{*,1}, Michele Aragona ¹, Cosimo Rodia, Walter Baronti, Giovanni de Gennaro, Alessandra Bertolotto, Stefano Del Prato

Department of Clinical and Experimental Medicine, Section of Diabetes and Metabolic Diseases, University of Pisa - Azienda Ospedaliero Universitaria Pisana, Pisa, Italy

ARTICLE INFO

Article history:

Received 16 August 2018

Received in revised form 13 September 2018

Accepted 16 October 2018

Available online 24 October 2018

Keywords:

Freestyle Libre

Flash glucose monitoring

Diabetes management

Insulin dose adjustment

Trend arrows

ABSTRACT

Freestyle Libre (FSL) system is a new method to detect glucose enabling a new paradigm in glucose monitoring and self-management. The sensor, reading the interstitial fluid glucose concentration, provides a numerical data of glucose level and a trend arrow that add context to static measurement of glucose level. Therefore, patients could easily follow the progression of their glucose levels over the time, allowing early detection and timely treatment of deviations from targeted glucose level range, thus preventing extreme fluctuations. In order to take full advantage of the system both the caregiver and the person with diabetes must appreciate the need of careful interpretation of the data generated by the FSL. To this purpose we have generated recommendations that are based on methods suggested for CGM, our clinical experience and discussion with experienced patients using FSL, to provide a pragmatic approach to use FSL trend arrow data for managing diabetes in adults.

© 2018 Elsevier Inc. All rights reserved.

Since the 1980s, numerous clinical studies have been performed to determine the benefit of optimal glycemic control for prevention of micro- and macrovascular complications in subjects with type 1 [T1DM]^{1,2} or type 2 [T2DM]³ diabetes.

HbA1c is commonly used for assessing glycemic control and reducing the risk of long term diabetic complications. This benchmark marker measures the average glucose exposure over the past 2–3 months, but cannot detect short-term changes in blood glucose nor it allows quantification of time spent with hypo- and hyperglycemia nor glycemic variability. Therefore, HbA1c measurements have to be supplemented by alternative glucose parameters.

Capillary blood glucose monitoring (CBGM) is commonly used for adapting glucose-lowering therapy to lifestyle (diet and physical activity) and individual needs (school, work, holidays, illness), and it facilitates identification and treatment of acute hypo - and hyperglycemic swings.^{4–6} Nonetheless, optimizing glucose levels can be hard, particularly in patients on intensive insulin therapy requiring frequent capillary blood glucose testing (≥ 4 controls daily). Fingertip pricking, the need of

a meter and disposable supplies and the search for a private place to check blood glucose can become hurdles to a regular glucose self-monitoring with deleterious consequences on glycemic control.^{4–6} Moreover, even when CBGM is carefully performed, critical fluctuations in glucose levels may go unnoticed. Continuous Glucose Monitoring (CGM) can, to some extent, overcome such limitation. This is based on measurement of glucose concentration in the interstitial fluid at high sampling frequency (e.g., every 5 min) and helps recognizing otherwise undetectable events (in particular, non-symptomatic hypoglycemic episodes). CGM can be divided into two categories: 1. Blinded retrospective analysis of CGM for identification of glucose patterns to guide changes in therapy or 2. Real-time CGM recording and displaying current glucose value along with trends and rate of change. The latter can be equipped with alarms to alert the person with diabetes at the time of hyper/hypoglycemia. Several randomized controlled trials (RCTs) have evaluated the potential benefit of CGM.^{7–13} Though these devices may sound intuitive, a proper educated use to guide therapeutic decisions is not trivial, and over the past years, a number of different algorithms (Table 1) have been proposed for adjusting insulin dose based on glucose trend as detected by CGM.^{14–19}

Most recently, a third category of glucose monitoring systems (FreeStyle Libre, FSL, Abbott Diabetes Care, Alameda, CA) with no alarm has been introduced. Like CGM, FSL provides real-time interstitial glucose levels as well as trends (indicated by trend arrows). FSL offers an alternative glucose monitoring strategy for comprehensive analysis of glucose profile without the inconvenience of capillary glucose testing. RCTs and real life data show that in patients with T1DM or insulin-

Potential conflict of interest: CB received honoraria for consulting fees from Eli Lilly. SDP has served on the scientific board and received honoraria for consulting fees from Astra Zeneca; Boehringer Ingelheim; Eli Lilly; GlaxoSmithKline; Merck & Co.; Novartis Pharmaceuticals; Novo Nordisk; sanofi; servier; Takeda Pharmaceuticals. No other potential conflicts of interest relevant to this article were reported.

* Corresponding author at: University Hospital of Pisa, Department of Medical Area, Section of Metabolic Diseases and Diabetes, Via Paradisa, 2, 56124 Pisa, Italy.

E-mail address: c.bianchi@ao-pisa.toscana.it (C. Bianchi).

¹ Cristina Bianchi and Michele Aragona are equal first authors.

Table 1

Previous methods to adjust insulin doses using CGM trend arrows.

Trend arrows	DirecNet ¹⁴	Scheiner ¹⁵	Pettus/Edelman ¹⁶	Aleppo ¹⁷	
↑↑	20% increase of total dose	Increase to cover current sensor glucose plus 60 mg/dl	Increase to cover current sensor glucose plus 100 mg/dl	CF	IDA
				<25	+4.5
				25–<50	+3.5
				50–<75	+2.5
				≥75	+1.5
↑	20% increase of total dose	Increase to cover current sensor glucose plus 30 mg/dl	Increase to cover current sensor glucose plus 75 mg/dl	<25	+3.5
				25–<50	+2.5
				50–<75	+1.5
				≥75	+1.0
↗	10% increase of total dose	Cover current sensor glucose	Increase to cover current sensor glucose plus 50 mg/dl	<25	+2.5
				25–<50	+1.5
				50–<75	+1.0
				≥75	+0.5
→	0% increase	Cover current sensor glucose	Cover current sensor glucose	<25	No adjustment
				25–<50	No adjustment
				50–<75	No adjustment
				≥75	No adjustment
↘	10% decrease of total dose	Cover current sensor glucose	Decrease to cover current sensor glucose minus 50 mg/dl	<25	–2.5
				25–<50	–1.5
				50–<75	–1.0
				≥75	–0.5
↓	20% decrease of total dose	Decrease to cover current sensor glucose minus 30 mg/dl	Decrease to cover current sensor glucose minus 75 mg/dl	<25	–3.5
				25–<50	–2.5
				50–<75	–1.5
				≥75	–1.0
↓↓	20% decrease of total dose	Decrease to cover current sensor glucose minus 60 mg/dl	Decrease to cover current sensor glucose minus 100 mg/dl	<25	–4.5
				25–<50	–3.5
				50–<75	–2.5
				≥75	–1.5

treated T2DM, the use of FSL, compared to CBGM, increases the frequency of self-monitoring, reduces the time spent in hypo- and hyperglycemia, as well as the number of symptomatic hypoglycemic events, increases the time spent in the optimal glucose range, and improves the quality of life for people with diabetes,^{20–28} though any improvement of HbA1c has been observed.^{20,28} The reduced time spent in hypoglycaemia suggests that real-time and glucose trend data, rather than retrospective analysis of the recordings, were predominantly used for proactive self-adjustments of glycaemic control, however further information for FSL user and physician may be acquired from the retrospective analysis of FSL readings and used to improve insulin therapy. A critical aspect of FSL is the correct interpretation of the trend arrows as this has the potential for avoiding major hypo-hyperglycemic fluctuations. For the person with diabetes this is sort of a novel approach requiring ad hoc guidance. However, to date no practical approach to using trend arrows on the FSL for the management of adults with diabetes have been developed.

Therefore, after reviewing published methods suggested for CGM,^{14–17} discussing with FSL users about the correct interpretation of static and dynamic information derived from the system and patients reported outcomes, on the basis of our clinical experiences as diabetologists, we developed a practical, patient-centered approach to adjust insulin doses based on trend arrow FSL data in relationship to pre-meal or between meal time.

1. The FreeStyle Libre system

The Free Style Libre (FSL) system allows ‘flash glucose determination and monitoring’ by wireless scanning of a transmitter connected with a sensor filament, which is inserted 5 mm under the skin for accurate measurement of glucose in the interstitial fluid. The sensor can be interrogated through clothes and is water resistant and it can be worn while swimming and bathing. The scanner shows historical and current glycaemic trends and integrates blood glucose readings in a number of different manner (daily profiles, mean glucose values, daily variability, time spent within a pre-defined range, hypoglycemic events, and sensor performance). As compared to the CGM, FSL has no alarms making it not

suitable for patients unable to recognize signs and symptoms of hypoglycemia. Nonetheless, for all other patients, acceptance of the device and use persistence can be increased, as the presence of too many alarms is a common reason for discontinuation CGM.²⁹ Finally, the FSL has been proved to be safe and accurate in pregnant woman with diabetes.³⁰

FSL is factory calibrated using wired enzyme technology (osmium mediator and enzyme glucose oxidase enzyme co-immobilized on an electrochemical sensor filament), resulting in accuracy metrics similar to other commercially available CGM system.^{31–36} Therefore, the FSL user is not required to perform calibration with capillary glucose measurement, although this may be recommended in case of hypoglycemia or rapid fluctuation of glucose concentration due the delay in glucose distribution in the interstitial fluid (13.5 min approximately). In the US, FSL has been approved for “non adjunctive use”, i.e. suitable for therapeutic decisions (insulin dosing) based on a mean absolute relative difference (MARD) between paired measurements with a reference method for blood glucose measurements <10%. In Europe, the FSL remains approved only as “adjunctive use”. A very recent study³⁷ highlights that although error grid analysis find almost all measurements to be clinically acceptable, one in four readings of both CGM and FSL differed from CBGM readings by at least 15 mg/dl and one in twenty values deviated by at least 30 mg/dl or 30%, potentially resulting in different therapeutic decision (i.e. carbohydrate intake and/or insulin delivery) and such deviation should be taken into account when using CGM or FSL systems.

Data collected by the FSL system can be sent to a dedicated app on an Android or iOS device, removing the need for a separate reader, and allowing remote monitoring of glucose readings and trends. The cost of the FSL is approximately one-half to one-third of other commercially available CGM systems.³⁸ All these features are the likely explanation of the wide diffusion of this system, which is currently used by >400,000 people across 40 countries.³⁸

2. Education principles and skills for FSL users

The FSL system can be easily applied through its own applicator, it is easy to use, allowing wide use even in an unselected diabetic population.

Table 2
Suggested approach to adjust insulin doses using FSL system trend arrows in adults with diabetes.

Trend arrows	Status ^a	Pre-meal time			Between-meal time		
		Hyperglycemia	Normoglycemia	Hypoglycemia	Hyperglycemia	Normoglycemia	Hypoglycemia
↑	Rate of glucose change ^b Increase >2 mg/dl/min	RD + correction bolus according to ISF considering current sensor glucose plus 60 mg/dl	RD + 20% if low risk of hypos or RD + 10% if high risk of hypos or faster insulin aspart use	• Confirm with CBGM • Corrected according to the 15–15 rule • Recheck after 30'	• Correct according to FSI considering current sensor glucose plus 60 mg/dl • Recheck after 1 h	• Recheck after 15–30' Correct according to the FSI if necessary	• Confirm with CBGM • Corrected according to the 15–15 rule • Add 15 g of slow-absorption carbohydrates • Recheck after 60'
↗	Increase 1–2 mg/dl/min	RD + correction bolus according to ISF considering current sensor glucose plus 30 mg/dl	RD if high risk of hypos or faster insulin aspart use	• Recheck after 30'	• Correct according to FSI considering current sensor glucose plus 30 mg/dl • Recheck after 1 h	• Recheck after 30–60' Correct according to the FSI if necessary	• Recheck after 60'
→	Change <1 mg/dl/min	RD + correction bolus according to ISF	RD		• Correct according to the FSI • Recheck after 1 h	Recheck after 1–2 h	
↘	Decrease 1–2 mg/dl/min	Recheck after 30'	• Correct according to 15–15 rule if necessary • Recheck after 30'		• Recheck after 30–60'	• Recheck after 30–60' Correct according to 15–15 rule if necessary	
↓	Decrease >2 mg/dl/min	Recheck after 15'	• Correct according to 15–15 rule if necessary • Recheck after 30'		Recheck after 30–60'	• Recheck after 30' • Correct according to 15–15 rule if necessary	

RD: recommended dose; ISF: correction bolus based on insulin sensitivity factor.

^a Status is defined by the static glucose level measurement, according with age, co-morbidity and fragility of the patients.

^b Rate of glucose change is derived by directionally dynamic trend arrows.

Nonetheless, in order to take full advantage of its features, people with diabetes do require ad hoc education.

This education process should include four main issues:

1. careful and reliable sensor insertion and tips to improve sensor adhesion and avoid premature detachments. Though other site different from the arm, such as gluteal region or leg, has been evaluated for the application of FSL, the best performance is that related to arm application.³⁹ Moreover, in about 10% of cases a skin irritation or redness may occur, impairing the correct glucose reading
2. awareness of the 5–10 minute lag time in glucose diffusion from the circulating compartment into the interstitial fluid. It is critical for the clinicians to make sure that their patients understand that data from FSL system will not always match up directly with blood glucose meter results, especially when glucose levels are changing rapidly;
3. remember that the FSL may require 24–48 h to reach reading equilibrium and it may become less precise in the last 24–48 h of its 14-day reading life. During these periods capillary blood glucose readings may be required;
4. correct interpretation of both static and dynamic data derived from the FSL system and how to use trend arrows in order to take educated treatment decisions to pursue individualized targets and intervention strategies (Table 2).
5. remind that the effectiveness of glucose monitoring depends largely on sufficient sensor utilization and that improvements in glucose control are rapidly reversed following cessation of monitoring,⁷ therefore almost 8 scans/daily are needed for a correct data interpretation.

2.1. FSL system application

Patients should follow the manufacture instructions about the choice of the site, skin cleansing, device preparation and sensor application. In case of irritation, glue allergy or adhesion issues, it is possible to create a barrier between the adhesive disc and the skin, reducing irritation and improving the adhesion of the devices. This can be achieved by using adhesive wipes, liquid protective film, or liquid medical adhesive. In the case of physical activity or for person who sweat conspicuously, it is advisable to apply a strip of taping tape (i.e. kinesthesia patch) over the sensor. The sensor is water resistant but if exposure to water is prolonged protect it with an impermeable band.

3. Interpretation of dynamic data collected by FSL system and use of trend arrows to adjust insulin dose or avoid hypoglycemia

The interpretation of the dynamic data of FSL system places the T1DM and insulin-treated T2DM patients in front of more complex decisions compared to the traditional static data provided by CBGM. The patient should be able to evaluate both absolute glucose level applying common rules of correction of hyper/hypoglycemia as well as the trend arrow. The shift from “point-in-time” glucose monitoring to “anticipation” of glucose changes is a feature of FSL. Sometimes the FSL system does not generate trend arrows either because glycemia varies too fast or because the system detects very discordant measurements. In this case it is important evaluation of the trend graph can be of assistance if the graph shows a downward trend, most likely the blood sugar is decreasing, conversely if the curve tendency is upward, the blood sugar is increasing.

Obviously, treatment (insulin dose) adjustment must take into account all standard parameters, such as insulin-to-carbohydrate ratio, Insulin Sensitivity Factor (ISF) or Correction Factor (CF), meal composition, time since last meal and last insulin injection, and exercise. On top of all this, the directionality of trend arrows can provide additional guidance, allowing “anticipation” of glucose changes that can translate into an opportunity to proactively adjust insulin dose (Table 3), prevent hypoglycemia, and achieve a more stable circadian glycemic control. To this

Table 3

Example of patient guide for insulin dose adjustment using the FSL system trend arrows.

Meal carbs	Insulin/carb ratio	RD (meal time insulin units)	Glucose reading before meal	Trend arrow	Correction dose according to ISF in case of hyperglycemia	Correction dose according with ISF in case of normoglycemia	Total insulin dose
				↑	(GR ___ mg/dl + 60 mg/dl) – GT ___ mg/dl/ISF ___ = ___ units	+20% (= ___ units)	
				↗	(GR ___ mg/dl + 30 mg/dl) – GT ___ mg/dl/ISF ___ = ___ units	+10% (= ___ units)	
				→	GR ___ mg/dl – GT ___ mg/dl/ISF ___ = ___ units	None	
				↘	None	None	
				↓	None	None	

RD: recommended dose; ISF: correction bolus based on insulin sensitivity factor; GR: glucose reading; GT: individualized pre-meal optimal glucose value.

purpose the following recommendations may provide guidance to the patient.

3.1. Pre-meal time glucose level and trend evaluation

NORMOGLYCEMIA (100–140 mg/dl)

• ↑ UPWARD TREND ARROW

Glucose increase is rapid (>2 mg/dl/min). The patient should consider that, within 30 min (i.e. the required for injected rapid insulin analog to start exerting its glucose lowering effect) glucose level could increase by ≥60 mg/dl. In such a case it would be appropriate a 20% increase of the insulin dose, if the patient is not prone to hypoglycemia, while a 10% increase may be more suitable in subjects at high risk of hypoglycemia^{12,22,40} or for patients using faster aspart insulin.⁴¹

• ↗ UPWARD-OBLIQUE TREND ARROW

Rate of glucose increase is less pronounced (1–2 mg/dl/min). The FSL user should consider that, within 30 min (i.e. the required for injected rapid insulin analog to start exerting its glucose lowering effect) glucose level could increase by 30–60 mg/dl. In this case 10% increase in insulin dose is appropriate for a patient not prone hypoglycemia. No insulin dose adjustment should be considered for subjects at high risk of hypoglycemia or for patients treated with faster aspart insulin.⁴¹

• → HORIZONTAL TREND ARROW

Glucose values are stable (<1 mg/dl/min change). Dose of insulin should be calculated as usual on the basis of carb-counting and usual standard parameters previously described.

• ↘ DOWNWARD-OBLIQUE TREND ARROW

Rate of glucose decrease is modest (1–2 mg/dl/min). FSL user should consider that, within 30 minute glucose levels could be reduced by 30–60 mg/dl. No insulin adjustment should be considered, but for patients prone to hypoglycemia glucose administration according to the 15-15 rule (see below) could be considered.

• ↓ DOWNWARD TREND ARROW

Rate of glucose decrease is rapid (>2 mg/dl/min). FSL user should consider that, within 30 minute glucose levels could be reduced by 60 mg/dl or more. In this case patient should consider glucose administration according to the 15-15 rule (see below).

HYPERGLYCEMIA (>140 mg/dl)

• ↑ UPWARD TREND ARROW

Glucose increase is rapid (>2 mg/dl/min). FSL user should consider that glucose level is already high and it will increase further by 60 mg/dl or more within 30 min. Patient should calculate the insulin dose adjustment based on the ISF adding 60 mg/dl to the glucose level indicated by FSL system. In case of severe hyperglycemia (>250 mg/dl) a CBGM confirmation and a ketones check could be useful, especially if reading is done in the morning, after night time fasting. In the case of

ketosis, patient should contact the physician. If ketones are absent, patient should calculate the insulin dose adjustment based on the ISF adding 60 mg/dl to the glucose level indicated by FSL, and wait almost 60 min without eating. An adequate hydration should be recommended, if not contraindicated (i.e. heart failure). Then, patient should scan again and revalue the situation.

• ↗ UPWARD-OBLIQUE TREND ARROW

Glucose increase is modest (1–2 mg/dl/min). FSL user should consider that glucose level is already high, tends to a further increase and it will increase further by 30–60 mg/dl within 30 min. Patient should calculate the insulin dose adjustment based on the ISF adding 30 mg/dl to the glucose level indicated by FSL system. In case of severe hyperglycemia (>250 mg/dl) a CBGM confirmation and a ketones check could be useful, especially if reading is done in the morning, after night time fasting. In the case of ketosis, patient should contact the physician. If ketones are absent, patient should calculate the insulin dose adjustment based on the ISF adding 30 mg/dl to the glucose level indicated by FSL, and wait almost 30–60 min without eating. An adequate hydration should be recommended, if not contraindicated (i.e. heart failure). Then, patient should scan again and revalue the situation.

• → HORIZONTAL TREND ARROW

Glucose values are stable (<1 mg/dl/min change), but glucose levels are it will remain if not slightly increase before the next meal. FSL user may consider an insulin dose adjustment calculated on the basis of ISF or CF in order to aim at a pre-meal glucose value <140 mg/dl. In case of severe hyperglycemia (>250 mg/dl) a CBGM confirmation and a ketones check could be useful, especially if reading is done in the morning, after night time fasting. In the case of ketosis, patient should contact the physician. If ketones are absent, patient should calculate the insulin dose adjustment based on the ISF, and wait almost 30–60 min without eating. An adequate hydration should be recommended, if not contraindicated (i.e. heart failure). Then, patient should scan again and revalue the situation.

• ↘ DOWNWARD-OBLIQUE TREND ARROW

Glucose is high, but is slowly decreasing (1–2 mg/dl/min). It is advisable to wait and recheck glucose value again after 30 min. In case of severe hyperglycemia (>250 mg/dl) a CBGM confirmation and a ketones check could be useful, especially if reading is done in the morning, after night time fasting. In the case of ketosis, patient should contact the physician. If ketones are absent, patient should calculate the insulin dose adjustment based on the ISF subtracting 30 mg/dl to the glucose level indicated by FSL, and wait almost 30–60 min before eating. An adequate hydration should be recommended, if not contraindicated (i.e. heart failure).

• ↓ DOWNWARD TREND ARROW

Glucose is high, but is rapidly decreasing (>2 mg/dl/min). It is advisable to wait and recheck glucose value again after 30 min. In case of severe hyperglycemia (>250 mg/dl) a CBGM confirmation and a ketones

check could be useful, especially if reading is done in the morning, after night time fasting. In the case of ketosis, patient should contact the physician. If ketones are absent, patient should calculate the insulin dose adjustment based on the ISF subtracting 60 mg/dl to the glucose level indicated by FSL, and wait almost 30 min before eating. An adequate hydration should be recommended, if not contraindicated (i.e. heart failure).

HYPOGLYCAEMIA (<100 mg/dl)

Regardless the direction of the trend arrow, hypoglycemia must always be confirmed with a CBGM (3C rule, see below) and corrected with rapidly absorbed carbohydrate (sugars), according to the 15-15 rule (see below) if CBGM is <70 mg/dl, or with 5 g of rapidly absorbed carbohydrate (sugars) if CGBM is between 70 and 100 mg/dl, to avoid swing up and hyperglycemia. Moreover, FSL users should confirm recovery from hypoglycemia by CBGM, because the FSL could take longer to confirm achievement of normoglycemia, leading to overcorrection. A glucose reading should be obtained again 30 min after normoglycemia has been achieved and insulin dose calculated according to such a reading.

3.2. Between-meal time glucose level and trend evaluation

The glycemic variations between meals are generally limited, except in case of intense physical activity or ingestion of snacks containing rapidly absorbed carbohydrates. Trend arrows direction can help FSL avoiding excessive hypoglycemia.

NORMOGLYCEMIA (100–180 mg/dl)

• ↑ UPWARD TREND ARROW

Glucose increase is rapid (>2 mg/dl/min). FSL user should consider that, within 30 minute glucose level could increase by 60 mg/dl or more. In this case, the patient should re-check glucose level after 15–30 min and if still increasing an additive insulin bolus calculated according to ISF and insulin on board should be considered.

• ↗ UPWARD-OBLIQUE TREND ARROW

Glucose increase is modest (1–2 mg/dl/min). FSL user should consider that, within 30 minute glucose level could increase by 30–60 mg/dl. In this case patient should re-check glucose level after 30–60 min and if still increasing an additive insulin bolus calculated according to ISF and insulin on board should be considered.

• → HORIZONTAL TREND ARROW

Glucose levels are well controlled and stable. Re-check glucose level after 1–2 h.

• ↘ DOWNWARD-OBLIQUE TREND ARROW

Glucose decrease is modest (1–2 mg/dl/min). FSL user should consider that, within 30 minute glucose level could decrease by 30–60 mg/dl. In this case patient should re-check glucose level after 15–30 min and if still decreasing or reaching a value ≤100 mg/dl treating the glucose level as a hypoglycemia, correcting according with the 15-15 rule to prevent further decrease, overall if physical activity has been done or planned.

• ↓ DOWNWARD TREND ARROW

Glucose is high, but is rapidly decreasing (>2 mg/dl/min). FSL user should consider that, within 30 minute glucose levels could be reduced by 60 mg/dl or more. In this case patient should consider treating the glucose level as a hypoglycemia, correcting according with the 15-15 rule, overall if physical activity has been done or planned.

HYPERGLYCEMIA (>180 mg/dl)

• ↑ UPWARD TREND ARROW

Glucose increase is rapid (>2 mg/dl/min). FSL user should consider that glucose level is already high and it will increase by 60 mg/dl or

more within 30 min. Patient should consider injecting a rapid insulin bolus calculated according to ISF adding 60 mg/dl to the glucose value indicated by FSL and considering the insulin on board in case the reading has been done into 2–4 h after meal. Re-check glucose level and the trend after 1 h. In case of severe hyperglycemia (>250 mg/dl) a CBGM confirmation could be useful. An extra insulin bolus, calculated according to ISF adding 60 mg/dl to the glucose value indicated by FSL, should be injected. A new glucose scan should be performed after 60 min to revalue the situation. Patient should be advised to take into account the insulin on board of the correction bolus at the time of subsequent insulin injection.

• ↗ UPWARD-OBLIQUE TREND ARROW

Glucose increase is modest (1–2 mg/dl/min). FSL user should consider that glycemia is already high and it will increase by 30–60 mg/dl within 30 min. Patient should consider injecting a rapid insulin bolus calculated according to ISF adding 30 mg/dl to the glucose value indicated by FSL and considering the insulin on board in case the reading has been done into 2–4 h after meal. Re-check glucose level and the trend after 1 h. In case of severe hyperglycemia (>250 mg/dl) a CBGM confirmation could be useful. An extra insulin bolus, calculated according to ISF adding 30 mg/dl to the glucose value indicated by FSL, should be injected. A new glucose scan should be performed after 60 min to revalue the situation. Patient should be advised to take into account the insulin on board of the correction bolus at the time of subsequent insulin injection.

• → HORIZONTAL TREND ARROW

Glucose value is stable (1–2 mg/dl/min), but glucose level is high. Patient should consider injecting a rapid insulin bolus calculated according to ISF and considering the insulin on board in case the reading has been done into 2–4 h after meal. In case of severe hyperglycemia (>250 mg/dl) a CBGM confirmation could be useful. An extra insulin bolus, calculated according to ISF, should be injected. A new glucose scan should be performed after 60 min to revalue the situation. Patient should be advised to take into account the insulin on board of the correction bolus at the time of subsequent insulin injection.

• ↘ DOWNWARD-OBLIQUE TREND ARROW

Glucose is high, but is slowly decreasing (1–2 mg/dl/min). It is advisable to wait and recheck glucose value again after 30–60 min. Patient should consider that, within 30 minute glucose level could decrease by 30–60 mg/dl, therefore in case of glucose value close to the target (~140 mg/dl), a further scan should be suggested in 15–30 min. On the contrary, in case of severe hyperglycemia (>250 mg/dl) a CBGM confirmation could be useful. An extra insulin bolus, calculated according to ISF subtracting 30 mg/dl to the glucose value indicated by FSL, should be injected. A new glucose scan should be performed after 60 min to revalue the situation. Patient should be advised to take into account the insulin on board of the correction bolus at the time of subsequent insulin injection.

• ↓ DOWNWARD TREND ARROW

Glucose is high, but is rapidly decreasing (>2 mg/dl/min). It is advisable to wait and recheck glucose value again after 30 min. Patient should consider that, within 30 minute glucose level could decrease by 60 mg/dl or more, therefore in case of glucose value close to the target (~140 mg/dl), a further scan should be suggested in 15–30 min and eventually a snack with 15 g of complex carbohydrates (i.e. two crackers or 20 g of bread) should be taken. On the contrary, in case of severe hyperglycemia (>250 mg/dl) a CBGM confirmation could be useful. An extra insulin bolus, calculated according to ISF subtracting 60 mg/dl to the glucose value indicated by FSL, should be injected. A new glucose scan should be performed after 60 min to revalue the situation. Patient should be advised to take into account the insulin on board of the correction bolus at the time of subsequent insulin injection.

HYPOGLYCAEMIA (<100 mg/dl)

Regardless the direction of the trend arrow, hypoglycemia must always be confirmed with a CBGM (3C rule, see below). In case of CBGM <70 mg/dl patient should correct with rapidly-absorbed carbohydrate (sugars), according to the 15-15 rule (see below), while 5 g of rapidly absorbed carbohydrate may be sufficient if CBGM is between 70 and 100 mg/dl, to avoid swing up and hyperglycemia. Moreover, 15 g of slow-absorption carbohydrates should be taken in order to stabilize glycemia until the next meal, since insulin is still present in the circulation and not completely metabolized. FSL users should be advised to confirm recovery from hypoglycemia with CBGM, because the FSL could take longer to confirm achievement of normoglycemia, leading to overcorrection. A glucose reading should be obtained again 30 min after normoglycemia has been achieved and insulin dose calculated according to such a reading.

3.3. Night time glucose level

The glycemic variations during the night are generally limited. However, insufficient carbohydrates assumption or intense and prolonged physical activity during the day time may cause a nocturnal hypoglycemia.

In case of nocturnal hypoglycemia, FSL user should remember the 3C rule, therefore a CBGM confirmation and opportune correction are needed, according with glucose level (15-15 rules). After recovery, documented with CBGM, 15 g of complex carbohydrates should be taken to neutralizing the insulin on board and glucose value re-checked with CBGM after 30–60 min.

A retrospective observation of repeated prolonged nocturnal hypos should address the FSL user to evaluate, according with the physician, a dose reduction of basal insulin and/or the choice of a newer basal insulin analogue characterized by both, a lower incidence of nocturnal hypos⁴² and major flexibility in time of injection (any time of the day).

However, in case of repeated awareness nocturnal hypos, an alarmed CGM should be suggested.

3.4. Hypoglycemia correction: 3C rule and 15-15 rule

In case of hypoglycemia, FSL user should be advised to follow the 3C rule: *Confirm* the hypoglycemia by CBGM, *Correct* according with 15-15 rule and *Check* again glucose level with CBGM. FSL users should use 15–20 g glucose as preferred treatment in case of blood glucose ≤70 mg/dl [3.9 mmol/L]), although any form of carbohydrate that contains glucose may be used, while 5 g of rapidly absorbed carbohydrate may be sufficient if CBGM is between 70 and 100 mg/dl. Fifteen minutes after treatment, if CBGM shows continued hypoglycemia, the same treatment should be repeated. Patients should be advised not to snack until their FSL glucose levels approach the target value, because of the lag-time, to avoid over-correction. Only once CBGM returns to normal, the person should ingest meal or snack (15 g of complex carbohydrates, i.e. two crackers or 20 g of bread) to prevent recurrence of hypoglycemia.⁴³

4. Inappropriately behaviors and pitfalls with FSL

The relative low cost of FSL led to a wide diffusion of this system, also among unselected subjects, with consequent improper use of the device. The simplicity of use and unnecessary fingertip pricking can lead both, an excessive number of scans with consequent inappropriate corrections or too low scans (like a traditional CBGM), not allowing to fully exploit the potentiality of the FSL. Moreover, because FSL is cheaper than CGM, also patients unable to recognize signs and symptoms of hypoglycemia, who instead need an alarmed system, could inadequately choose this device.

Finally, beside to the inappropriate use of FSL, some pitfalls should be considered to avoid that the system become “unsafe”. For example, aesthetic reasons as the visibility of the device may induce patients to

choice unsuitable, not recommended and therefore not reliable application sites. Moreover, although FSL is considered accurate, to date there are not enough data in clinical practice on the safety of “non adjunctive use” of FSL, therefore, actually we recommend confirmation by CBGM of extreme glucose values (hypos or severe hyperglycemia) before therapeutic decisions.

5. Conclusive considerations

SL system is a new method to detect glucose enabling a new paradigm in glucose monitoring and self-management. Patients could easily follow the progression of their glucose levels over the time, allowing early detection and timely treatment of deviations from targeted glucose level range, thus preventing extreme fluctuations. Improved glycaemic control and avoidance of repeated daily finger sticks will help ensuring improved quality of life. However, in order to take full advantage of the system both the caregiver and the person with diabetes must appreciate the need of careful interpretation of the data generated by the FSL. To this purpose we have generated recommendations that are based on methods suggested for CGM, our clinical experience and discussion with experienced patients using FSL. Our recommendations have a pragmatic value but no formal evaluation in proper clinical trial. Insulin-treated diabetes still implies a complex management but we hope our pragmatic approach may help patients to improve glucose control.

References

- Service FJ, O'Brien PC. The relation of glycaemia to the risk of development and progression of retinopathy in the Diabetic Control and Complications Trial. *Diabetologia* 2001;44:1215–20.
- Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–53.
- Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–12.
- Miller KM, Beck RW, Bergenstal RM, et al. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. *Diabetes Care* 2013;36:2009–14.
- Elgart JF, Gonzalez L, Prestes M, et al. Frequency of self-monitoring blood glucose and attainment of HbA1c target values. *Acta Diabetol* 2016;53:57–62.
- Schütt M, Kern W, Krause U, et al. Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. *Exp Clin Endocrinol Diabetes* 2006;114:384–8.
- Battelino T, Phillip M, Bratina N, et al. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care* 2011;34:795–800.
- Deiss D, Bolinder J, Riveline JP, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using realtime continuous glucose monitoring. *Diabetes Care* 2006;29:2730–2.
- The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–76.
- Šoupal J, Petruželková L, Flekač M, et al. Comparison of different treatment modalities for type 1 diabetes, including sensor-augmented insulin regimens, in 52 weeks of follow-up: a COMISAIR study. *Diabetes Technol Ther* 2016;18:532–8.
- Battelino T, Conger I, Olsen B, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* 2012;55:3155–62.
- Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections. The GOLD Randomized Clinical Trial. *JAMA* 2017;317:379–87.
- Beck RW, Riddlesworth T, Ruedy K, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections the DIAMOND Randomized Clinical Trial. *JAMA* 2017;317:371–8.
- Buckingham B, Xing D, Weinzimer S, Fiallo-Scharer R, Kollman C, Mauras N, et al. Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator). *Pediatr Diabetes* 2008;9:142–7.
- Scheiner G. *Practical CGM: Improving Patient Outcomes Through Continuous Glucose Monitoring*. 4th ed. Alexandria, VA: American Diabetes Association. 2015.
- Pettus J, Edelman SV. Recommendations for using real-time continuous glucose monitoring (rtCGM) data for insulin adjustments in type 1 diabetes. *J Diabetes Sci Technol* 2017;11:138–47.
- Aleppo G, Laffel LM, Ahmann AJ, et al. A practical approach to using trend arrows on the Dexcom G5 CGM system for the management of adults with diabetes. *J Endocr Soc* 2017;1:1445–60.

18. Laffel LM, Aleppo G, Buckingham BA, et al. A practical approach to using trend arrows on the Dexcom G5 CGM system to manage children and adolescents with diabetes. *J Endocr Soc* 2017;1:1461–76.
19. Klonoff DC, Kerr D. A simplified approach using rate of change arrows to adjust insulin with real-time continuous glucose monitoring. *J Diabetes Sci Technol* 2017;11:1063–9.
20. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, et al. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet* 2016;388:2254–63.
21. Reddy M, Jugnee N, El Laboudi A, et al. A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with Type 1 diabetes and impaired awareness of hypoglycaemia. *Diabet Med* 2018;35:483–90.
22. Haak T, Hanaire H, Ajjan R, et al. Use of flash glucose-sensing technology for 12 months as a replacement for blood glucose monitoring in insulin-treated type 2 diabetes. *Diabetes Ther* 2017;8:573–86.
23. Dover AR, Stimson RH, Zammit NN, et al. Flash glucose monitoring improves outcomes in a type 1 diabetes clinic. *J Diabetes Sci Technol* 2017;11:442–3.
24. McKnight JA, Gibb FW. Flash Glucose Monitoring is associated with improved glycaemic control but use is largely limited to more affluent people in a UK Diabetes Centre. *Diabet Med* 2017;34:732.
25. Ish-Shalom M, Wainstein J, Raz I, et al. Improvement in glucose control in difficult-to-control patients with diabetes using a novel flash glucose monitoring device. *J Diabetes Sci Technol* 2016;10:1412–3.
26. Holcombe A, Karunakaran V, Streeting J, et al. *Trial of FreeStyle Libre in a local service: impact on diabetes outcomes.* *Diabet Med* 2017;34:160. (P418).
27. Campbell FM, Murph NP, Stewart C, et al. Outcomes of using flash glucose monitoring technology by children and young people with type 1 diabetes in a single arm study. *Pediatr Diabetes* 2018;19:1294–301.
28. Oskarsson P, Antuna R, Geelhoed-Duijvestijn P, et al. Impact of flash glucose monitoring on hypoglycaemia in adults with type 1 diabetes managed with multiple daily injection therapy: a pre-specified subgroup analysis of the IMPACT randomised controlled trial. *Diabetologia* 2018;61:539–50.
29. Wong JC, Maahs DM, et al. Real time continuous glucose monitoring among participants in the T1D exchange clinic registry. *Diabetes Care* 2014;37:2702–9.
30. Scott EM, Bilous RW, Kautzky-Willer A. Accuracy, user acceptability, and safety evaluation for the FreeStyle Libre flash glucose monitoring system when used by pregnant women with diabetes. *Diabetes Technol Ther* 2018;20:180–8.
31. Aberer F, Hajnsek M, Rumpler M, Zenz S, et al. Evaluation of subcutaneous glucose monitoring systems under routine environmental conditions in patients with type 1 diabetes. *Diabetes Obes Metab* 2017;19:1051–5.
32. Gomez AM, Henao Carrillo DC, Munoz Velandia OM. Devices for continuous monitoring of glucose: update in technology. *Med Devices* 2017;10:215–24.
33. Bonora B, Maran A, Ciciliot S, et al. Head-to-head comparison between flash and continuous glucose monitoring systems in outpatients with type 1 diabetes. *J Endocrinol Invest* 2016;39:1391–9.
34. Ólafsdóttir A, Attvall S, Sandgren U, et al. A clinical trial of the accuracy and treatment experience of the flash glucose monitor FreeStyle Libre in adults with type 1 diabetes. *Diabetes Technol Ther* 2017;19:164–72.
35. Boscarì F, Galasso S, Acciaroli G, et al. Head-to-head comparison of the accuracy of Abbott FreeStyle Libre and Dexcom G5 mobile. *Nutr Metab Cardiovasc Dis* 2018;28:425–7.
36. Heinemann L, DeVries JH. Reimbursement for continuous glucose monitoring. *Diabetes Technol Ther* 2016;18:s248–52.
37. Freckmann G, Link M, Pleus S, Westhoff A, Kamecke U, Haug C. Measurement performance of two continuous tissue glucose monitoring systems intended for replacement of blood glucose monitoring. *Diabetes Technol Ther* 2018;20:541–9.
38. Abbott's Revolutionary Continuous Glucose Monitoring System. FreeStyle® Libre. 2018. now available to Medicare patients. PRNewswire. Available at: <https://www.prnewswire.com/news-releases/abbotts-revolutionary-continuous-glucose-monitoring-system-freestyle-libre-now-available-to-medicarepatients-300577201.html>. Accessed March 14, 2018.
39. Charleer S, Mathieu C, Nobels F, Gillard P. Accuracy and precision of flash glucose monitoring sensors inserted into the abdomen and upper thigh compared with the upper arm. *Diabetes Obes Metab* 2018;20:1503–7.
40. Hirsch IB. Algorithms for care in adults using continuous glucose monitoring. *J Diabetes Sci Technol* 2007;1:126–9.
41. Heise T, Pieber T, Danne T, Erichsen L, Haahr H. A pooled analysis of clinical pharmacology trials investigating the pharmacokinetic and pharmacodynamic characteristics of fast-acting insulin aspart in adults with type 1 diabetes. *Clin Pharmacokinet* 2017;56:551–9.
42. Heise T, Hövelmann U, Nosek L, Hermanski L, Böttcher SG, Haahr H. Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine. *Expert Opin Drug Metab Toxicol* 2015;11:1193–201.
43. America Diabetes Association. Glycemic targets: standards of medical care in diabetes 2018. *Diabetes Care* 2018;41:S55–64.