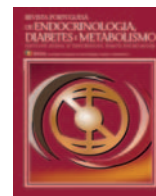




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Guidelines

National Consensus in the Use of the Flash Glucose Monitoring System in Portugal



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A B S T R A C T

Monitoring of glucose levels is essential in the management of diabetes, particularly in insulin therapy. The flash glucose monitoring system FreeStyle Libre® is an intermittent continuous monitoring system that adds a set of new data to the traditional blood glucose determinations and that, when properly used, can lead to better glucose control through more personalized and rigorous clinical advice, as well as greater involvement and responsibility of the patients in the management of their condition. The recommendations outlined here aim to guide and standardize clinical practice and communication with the patient, namely: 1) New parameters for glucose assessment 2) Reading and interpretation of the ambulatory glucose profile (AGP) and 3) Interpretation of trend arrows and therapeutic adjustments.

Consenso Nacional para a Utilização do Sistema de Monitorização Flash da Glicose em Portugal

R E S U M O

A monitorização dos níveis de glicose é essencial na gestão da diabetes, em particular em regimes terapêuticos com insulina. O sistema de monitorização flash da glicose FreeStyle Libre® é um sistema de monitorização contínua intermitente, que acrescenta um conjunto de novos dados às tradicionais determinações de glicose capilar e que, quando adequadamente utilizado, poderá conduzir a um melhor controlo da glicemia através de um aconselhamento clínico mais personalizado e rigoroso e de um maior envolvimento e responsabilização dos doentes. As recomendações aqui delineadas têm como objetivo orientar e uniformizar a prática clínica e a comunicação com o doente, nomeadamente no que diz respeito a: 1) Novos parâmetros de avaliação da glicose 2) Leitura e interpretação do perfil ambulatorio de glicose (AGP) e 3) Interpretação das setas de tendência e ajustes terapêuticos.

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Introduction

Diabetes mellitus (DM) is a chronic disease characterised by the presence of hyperglycaemia, which in turn leads to the development of macro- and microvascular complications. The treatment of DM includes different options - pharmaceutical and non-pharmaceutical - that aim to normalise blood glucose levels with the goal of not only preventing long-term vascular complications, but also to avoid the acute problems of day-to-day hyperglycaemia or hypoglycaemia. One approach to management, namely insulin therapy, requires knowledge of daily blood sugar levels to ensure that correct doses of insulin are administered. In the last 50 years, technologies have been introduced that allow us to easily assess blood-sugar levels and make appropriate adjustments to therapy.¹

Landmark clinical trials, including the United Kingdom Prospective Diabetes Study (UKPDS), Diabetes Control and Complications (DCCT) Trial and Epidemiology of Diabetes Intervention and Complications (EDIC) Trial, have shown that elevated glycated haemoglobin (HbA1c) levels are predictive for the risk of future complications.²⁻⁴ However, since HbA1c reflects the average plasma glucose concentration over the previous 3 months, it cannot supply any information on day-to-day glycaemic stability, the variability of blood glucose over time, the risk, number and severity of episodes of hypoglycaemia, or the existence of periods of postprandial hyperglycaemia. Self-monitoring of blood glucose (SMBG) can, if done regularly, provide part of this information; however, many people with diabetes find SMBG to be inconvenient and painful and do not monitor their levels regularly. Additionally, the information collected regarding control, glycaemic stability and the number and frequency of episodes of hypoglycaemia is often incomplete. In this context, tools that allow for the monitoring of glucose in the interstitial fluid - continuous glucose monitoring (CGM) - are invaluable for people with diabetes, both in terms of glucose control as well as comfort and quality of life.

The introduction of the FreeStyle Libre flash glucose monitoring system (Abbott Diabetes Care Ltd), and its subsequent reimbursement by the National Health Service in Portugal, provides another option for interstitial glucose monitoring. Extending the use of this new technology will build on the knowledge gained from traditional SMBG readings, especially with regard to variation in glucose profiles, as well as creating benefits for glucose control based on the increased functionality of the device, such as trend arrows.

This publication summarises the recommendations of a panel of Portuguese experts on the use of the FreeStyle Libre system, and is intended to contribute to the standardisation of clinical practice and communication with the patient. The panel included members of three different societies (the Portuguese Society of Diabetology [SPD], the Portuguese Society of Endocrinology, Diabetes and Metabolism [SPEDM] and the Portuguese Society of Internal Medicine [SPMI]) and consisted of seven doctors and one diabetes specialist nurse, who as a patient with type 1 diabetes mellitus (T1DM) provided the patients perspective. The panel convened during the first semester of 2018 to review the literature and discuss and formulate recommendations for the use of the FreeStyle Libre flash glucose monitoring system with particular focus on: 1) the parameters used in the monitoring of glucose levels; 2) reading and interpretation of the ambulatory glucose profile (AGP); 3) use of trend arrows for guiding therapeutic adjustments.

The FreeStyle Libre Flash Glucose Monitoring System

The FreeStyle Libre flash glucose monitoring system is an intermittent continuous glucose monitoring system that can be used

as a substitute for SMBG in the self-management of DM; it is indicated for measuring glucose levels in the interstitial fluid of people with DM aged over 4 years, including pregnant women. A sensor the size and shape of a small coin is applied to the posterior arm, which allows a small filament to measure interstitial glucose in the subcutaneous tissue. Each sensor remains active for a period of up to 14 days. A reader is used to scan the sensor to obtain instant information about current glucose levels, as well as the history of glucose readings over the previous eight hours. The reader also displays a trend arrow which indicates the direction and predicted rate of change in short-term glucose levels.⁵

The FreeStyle Libre system comes factory calibrated and does not require manual calibration with finger sticks to measure interstitial glucose levels. The AGP report generated by the FreeStyle Libre software complies with the recently published international consensus where it is recommended as a standard for visualisation of CGM to aid the clinical decision-making process for individuals with T1DM and Type 2 DM (T2DM).⁶ The AGP can be used both by health professionals and by people with diabetes or their carer to allow interpretation of results and facilitate dialogue and treatment review.

The IMPACT clinical trial in individuals with T1DM demonstrated a significant reduction of 38% ($p < 0.0001$) in the mean time in hypoglycaemia (<70 mg/dL) in participants who used the FreeStyle Libre system in comparison with those who used SMBG.⁷ This reduction was almost immediate, indicating a speedy adoption of the system, and was achieved without compromising HbA1c values. The participants who used the FreeStyle Libre system spent more time in the recommended target glucose range (70–180 mg/dL) than those who used SMBG [15.8 (2.9) vs 14.6 (2.9)] hours, $p = 0.0006$. The improvements observed - with respect to both hypoglycaemia and the time spent in the target range - were sustained throughout the six months of the trial. A subgroup analysis of individuals according to treatment modality, CSII or MDI, revealed similar results, confirming the clinical benefit of this system in both groups of individuals.⁸ Patients monitored their glucose levels using the flash glucose monitoring system more frequently compared to SMBG users (15.1 readings/day vs 5.6 checks/day). Patient satisfaction was also significantly higher in those using the flash system, compared to those using SMBG (adjusted between-group difference -0.24 [SE: 0.049]; $p < 0.0001$). No severe adverse events relating to the device were reported.⁷

The results of the IMPACT trial were consistent with those observed in the REPLACE trial, which involved people with T2DM on MDI. A significant reduction of 43% of time spent in hypoglycaemia (<70 mg/dL) was observed in users of FreeStyle Libre compared to the SMBG control group ($p = 0.0006$), a reduction that was achieved without a concomitant increase in HbA_{1c} levels.⁹ Access to their glycaemic profiles enabled users of the FreeStyle Libre system to achieve rapid improvements, which were maintained during a six-month extension of the trial. After 12 months, the time spent in hypoglycaemia (<70 mg/dL) was reduced by 50% ($p = 0.0002$), with no reported device-related severe adverse events.¹⁰

These results were confirmed, in a real-world context, using data collected from more than 50 000 users of the FreeStyle Libre device. Individuals were shown to scan their device an average of 16.3 times a day, and that higher rates of scanning were significantly associated with lower levels of estimated HbA_{1c}, less time spent in hypoglycaemia/hyperglycaemia and more time spent in the target glucose range.¹¹ It should be emphasised this

data showed that estimated HbA1c gradually decreases from 8.0% to 6.7% as the frequency of glucose readings increases from the lowest to the most frequent scanning groups (from 4.4 to 48.1 readings/day respectively; $p < 0.001$).¹¹ These results were subsequently confirmed by a wider analysis, which included over 237 000 users and more than 1.5 million sensors.^{12,13} Favourable results have also been demonstrated for use in pregnant women¹⁴ and paediatric patients.¹⁵

Monitoring of Glucose Levels: Beyond HbA1c to New Parameters

HbA1c levels are the established reference marker in the assessment of glycaemic control of DM. However, it is difficult to tailor this single measurement to the needs of each individual and additional parameters should be included to better reflect the dynamic nature of glycaemia. These include: the time spent in the target range; average glucose levels; the definition of and time spent in hypoglycaemia and hyperglycaemia; and various indices of glycaemic variability. This variability in glucose levels has been shown to increase reactive oxygen species and endothelial dysfunction, which are key components in the pathogenesis of diabetes complications.¹⁶ Clinical studies have shown that this variability is associated with increases in the risk of micro- and macrovascular complications in individuals with T1DM and T2DM, to a greater extent than general exposure to glucose.¹⁷⁻¹⁹ However, although the importance of glycaemic variability is well established in the literature, the same cannot be said of the definition of the parameters used to measure it. In fact, glycaemic variability is a complex measurement, characterised by a certain amplitude, duration and frequency. In a consensus published in December 2017, specialists recommended that glycaemic variability be preferably assessed by the coefficient of variation (CV) or standard deviation (SD) of mean glucose levels, and that it should be taken into account in the general glycaemic profile chart. A CV of 36% or above is associated with unstable glucose levels.⁶

Panel Recommendations

With regard to the parameters used in the monitoring of glucose, the panel formulated the following recommendations:

- According to publications by the American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology (ACE), and the Advanced Technologies & Treatments for Diabetes (ATTD), a glucose evaluation report should provide the following data: average glucose levels, estimated HbA1c levels, proportion of time spent in different glucose concentration ranges, exposure to hypoglycaemia (time and number of episodes of minimum duration of 15 minutes), CV and/or SD.^{6,20}

Recently eA1c is being replaced by the new term glucose management indicator (GMI) to reflect the fact that it is a measure derived from glucose values and can provide an indication of the current state of a person's glucose management but not always match closely a corresponding laboratory measured A1C.³⁸

The limits of the target ranges of glucose concentration should be adjustable according to the needs of each patient; one option would be to define hyperglycaemia as values above 180 mg/dL, hypoglycaemia as levels below 70 mg/dL, clinically significant hypoglycaemia as levels below 54 mg/dL, and the recommended target range as 70–180 mg/dL.

- Glycaemic variability is a complementary parameter to HbA1c levels in the monitoring of people with diabetes.

- The software associated with CGM systems, such as the FreeStyle Libre system, should provide a direct measurement of glycaemic variability that is easily interpretable by patients and health professionals.

Reading and Interpretation of the Ambulatory Glucose Profile

The standardisation of the approach to monitoring glucose levels is critical in the management of people with diabetes and may result in a better level of control for each individual. The introduction of CGM systems has further emphasised this need, as the information provided by these systems can be complex and hard to interpret. Mazze et al and the International Diabetes Center have developed an approach called the ambulatory glucose profile (AGP) which, in a visually clear and statistically detailed way, shows exposure to glucose, its variability, and the time in the target range, based on the data collected through SMBG or CGM over a specific period of time.^{21,22} International consensus recommendations have called for the use of the AGP as a standard report for analysing glucose data.⁶

An AGP report consists of three different parts: a summary of the descriptive statistics (which includes glucose exposure and variability, percentage of values in the target range as well as percentage of values below/far below and above/far above target, and the average number of readings per day during the period of data analysis); a graphic visualisation of a 'standard-day', in which all the collected data for a defined period is condensed and presented as if it had occurred in a single period of 24 hours. The AGP is constituted by a median line and by the curves corresponding to the 25th–75th percentiles, also termed the interquartile range (IQR) and the 10th–90th percentiles, also termed the interdecile range (IDR); as well as a summary of the glucose variation in each 'standard day' (which allows verification of the variability from day to day).^{23,24} The graphic representation of readings across a standard day is of unquestionable value, as it allows for the identification of patterns in glucose variation and problem areas where intervention may be possible. The median line shows the usual exposure to glucose, while the amplitude of areas determined by the percentile curves indicates glucose variability: the width of the 25th–75th percentile band around the median line indicates the "usual" variability, while the width of the 10th–90th percentile band indicates "occasional" variability.²⁵ Periods where the risk of hypoglycaemia is high or worse than usual correspond to the times when the 10th percentile line approaches or surpasses the minimum glucose concentration limit considered to define these episodes (usually 70 mg/dL).

In addition to the AGP report, the software associated with the Freestyle Libre system also has an additional information chart (Fig. 1). This divides the glucose variation in the AGP into four periods and indicates, for each of them: the probability of the patient entering hypoglycaemia; the proximity of the median to the therapeutic goal, and; the amplitude of the variability below the median. This indication is given through an intuitive colour code (green, yellow, red) and helps to identify trends and risk of hypoglycaemia and hyperglycaemia, as well as situations in which the administration of a corrective insulin bolus to address an elevated glucose may result in a higher risk of hypoglycaemia.²⁶

The use of the AGP for analysing data may improve glycaemic control by providing information in a systematic and intuitive way that allows for the identification of daily patterns of hypoglycaemia and/or hyperglycaemia. It is an important tool that can support the clinical decision process and facilitate doctor-patient communica-

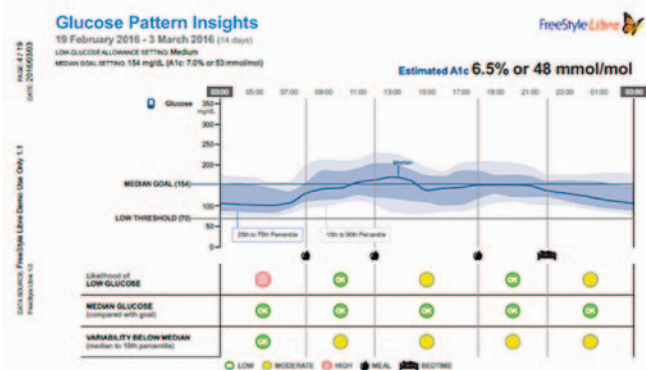


Figure 1. Example of an AGP as supplied by the Freestyle Libre device (Abbott), including the additional table that describes, for each period of the day, the probability of the individual incurring hypoglycaemia, the closeness of the median to the therapeutic goal, and the extent of the variability below the median [reproduced with permission].

tion, allowing the latter to visualise the effects of their behaviour and the therapeutic adherence to glucose control measures and, consequentially, a greater understanding of their diabetes treatment. International recognition of AGP has been accompanied by published recommendations which aim to guide the systematic analysis of AGP in the context of daily clinical practice. These recommendations usually take the form of an algorithm, which focuses essentially on three key steps: 1) analysing the quality of the collected data; 2) analysing the probability of hypoglycaemic periods; and 3) dividing the day into four parts for detailed analysis and discussion of each of them with the patient.^{6,25–27}

Panel Recommendations

The panel agrees that the analysis of the AGP report should focus on the following points: 1) quality of the data; 2) the target glucose range; 3) episodes of hypoglycaemia; 4) glucose variability; 5) the median curve and identification of glucose patterns; and 6) overall analysis of the exposure to glucose. In addition, the panel made the following specific recommendations for some of the points listed, namely:

• *Analysis of the quality of the data*

- In agreement with other consensus statements, the panel recommends that 14 days' worth of data with 70% or more of sensor data captured should provide an adequate quantity of information to interpret an AGP report. It is possible to make informative readings with fewer days; however, it should be kept in mind that overlapping days with very distinct patterns may dilute certain glycaemic trends and impair their correct visualisation.
- The days analysed in an AGP report should reflect the typical therapeutic daily routine, holidays, days with different work schedules, or periods of transition between different insulin schemes may influence the profile and, if needed, should be evaluated separately to determine patterns associated to these specific periods.
- It is important to note that the data collected by the sensor in the first hours of use may have a greater associated error due to insertion-site factors.

• *Determining the target range and associated time period*

- The standard target range is 70–180 mg/dL (or 70–140 mg/dL for pregnant women); however, this range should be tailored to the needs of each individual. The AACE recommends that

postprandial values can vary up to 140 mg/dL, while the American Diabetes Association (ADA) accepts variations up to 180 mg/dL. Thus, different values may be accepted according to the specific recommendations adopted.

- The time spent in the target range should be maximised, with a value above 70% being considered good; as with the target range limits, the objectives in terms of time spent in the target range may be adjusted to the requirements of each individual and other metrics such as mean glucose < 154 mg/dL or time in hypoglycaemia < 3% - 5% can also be considered as primary objectives, more easily attainable.

• *Analysis of hypoglycaemia episodes*

- The analysis of episodes of hypoglycaemia is particularly important, given the impact that these episodes have on the patient's health and quality of life, and as such should be priority when analysing the AGP reports. The analysis of these episodes should keep in mind their frequency and severity.
- Patients should be advised to confirm CGM glucose with capillary blood glucose in case of hypoglycaemia and to take into account that the accuracy of CGM systems is reported to be lower in hypoglycaemic range, potentially overestimating hypoglycaemia.

• *Analysis of glucose variability*

- The analysis of glucose variability should keep in mind the lifestyle of the patient. It is known that poor adherence to medication or lifestyles with variable routines (for example, individuals who work in shifts) can widen the amplitude of the IQR and IDR and complicate the process of counselling. In cases of individuals with very wide glucose variability, analysis of the daily glucose variation graphs may provide additional insights.

• *Analysis of the median curve and recognition of patterns*

- The median curve should be carefully analysed to identify patterns (for example, glucose spikes or characteristic curves between meals or in the nocturnal period); this information should be used for therapeutic reassessment and readjustment.

Interpretation of Trend Arrows and Therapeutic Adjustments

In general, adjustment of insulin doses is made after considering the following data: glucose levels, glucose target value, carbohydrate ingestion, and insulin calculation parameters (insulin/carbohydrate ratio and sensitivity factor). Traditionally, the glucose values used to trigger dose adjustment are obtained from SMBG, thus corresponding to a unique one-off value. However, the development of CGM systems has allowed the contextualisation of that value through the information present in the glucose variation profile and the trend arrows. The latter indicates the direction and speed of the change in glucose levels, taking into account the data collected in the most-recent 15 to 30 minutes before a measurement. This information has the potential to change the paradigm of therapeutic insulin adjustment, which can stop being based on a static measurement with no additional context and start being based on a forecast of glucose levels. However, to date no randomised clinical trials have been performed to determine the best way to incorporate information from trend arrows. Data has shown that trend arrows allow us to predict with accuracy what will happen in the next four hours, which has the potential to support assessment of safe glucose levels associated with driving.²⁸ The first postprandial hours and after insulin administration seem to be the moment where there may be less precision.²⁹ The precision of the two different systems – Dexcom G5 and FreeStyle

Libre - seem to be similar.³⁰ The recommendations that existed until now, briefly discussed below, are essentially based on the experience of experts, of people with diabetes, and on the few available clinical studies.³¹⁻³⁵

There are two types of recommendations for insulin dose adjustments based on trend arrows: the first recommendation is based on a percentage correction to the usual insulin doses, while the second takes into account the 'predicted' glucose value at the end of a set period of time. The first recommendation is derived from research by the Diabetes Research in Children Network (DirecNet): in this, the usual insulin dose should be increased at an increment of 10% or 20% when a fast or very fast (respectively) increase in glucose level is observed; conversely, a reduction of 10% or 20% should be applied to the inverse situation.³¹ The second recommendation, which adjusts the insulin according to the 'predicted' glucose level, is supported by evidence from several studies.³²⁻³⁵ These publications all recommend using an expected glucose level 30 to 45 minutes after the time of reading as the

basis for the insulin adjustment. The difference between them is in the way that this value is used to define the insulin adjustment. Pettus and Edelman suggest that the predicted glucose level be directly incorporated into the calculation of the dose, using the usual correction factor. The other authors present a simplified approach in which, through the use of averages and taking into account different ranges of insulin sensitivity, a value in insulin units is obtained which should be added or subtracted to the usual dose, depending on the direction of the trend arrows.³²⁻³⁵

It is worth noting that, despite the lack of data supporting these recommendations, people with diabetes actively use the information that is provided to them by the trend arrows for adjusting the therapeutic doses of insulin. A survey conducted in 2013 - before the publication of all the recommendations except those of DirecNet - showed that the majority of individuals, regardless of the type of diabetes or form of insulin therapy (MDI or CSII), used the trend arrows to adjust the insulin dose.^{36,37} Interestingly, and though there were differences between individuals with T1DM or T2DM, in both

Table 1. Proposed therapeutic steps for users in response to glucose readings and trend arrows displayed on the FreeStyle Libre system (Abbott) when in a pre-prandial state (before insulin is administered).

PRE-PRANDIAL TREND ARROWS WITHOUT ACTIVE INSULIN ¹					
WHENEVER AN ARROW IS RISING OR FALLING, THE REASON FOR THE OBSERVED CHANGE SHOULD ALWAYS BE SOUGHT ^{2,3}					
GLUCOSE LEVELS (mg/dL) (the glucose values indicated should be personalized)	↓	↘	→	↗	↑
	Rapidly falling glucose (> 2 mg/dL/min)	Falling glucose (between 1 and 2 mg/dL/min)	Stable glucose (changing <1 mg/dL/min)	Rising glucose (between 1 and 2 mg/dL/min)	Rapidly rising glucose (> 2 mg/dL/min)
	Fall >60 mg/dL after 30 min	Fall 30–60 mg/dL after 30 min	Change <30 mg/dL after 30 min	Rise 30–60 mg/dL after 30 min	Rise >60 mg/dL after 30 min
GLUCOSE >180 mg/dL	Do not administer a correction bolus	Do not administer a correction bolus	Take a correction bolus	Take a correction bolus based on the glucose value predicted by the arrow and aiming for the target glucose ³	Take a correction bolus based on the glucose value predicted by the arrow and aiming for the target glucose ³
THERAPEUTIC TARGET 70–180 mg/dL	Scan glucose after 30 min ²	Scan glucose after 30 min ²	Repeat reading after 30–60 min	Repeat reading after 15 min. If the trend continues, take a correction bolus based on the glucose value predicted by the arrow and aiming for the target glucose ³	Repeat reading after 15 min. If the trend continues, take a correction bolus based on the glucose value predicted by the arrow and aiming for the target glucose ³
LOW GLUCOSE <70 mg/dL	Have a meal with 30 g of CH without additional insulin if glucose <130 mg/dL ⁴	Have a meal with 15 g of CH without additional insulin if glucose is <130 mg/dL ⁴	Perform a fingerprick test	Perform a fingerprick test	Perform a fingerprick test
	Monitor glucose for 30 min ²	Monitor glucose for 30 min ²	Ingest 15 g of glucose if blood glucose <54 mg/dL	This situation will only occur following treatment of an earlier hypoglycaemia, so you should not ingest glucose and should monitor glucose for 30 min	This situation will only occur following treatment of an earlier hypoglycaemia, so you should not ingest glucose and should monitor glucose for 30 min
	Perform a fingerprick test	Perform a fingerprick test	If >54 mg/dL, ingest 10 g of CH		
	Ingest 15 g of glucose if blood glucose <70 mg/dL	Ingest 15 g of glucose if blood glucose <70 mg/dL	Monitor glucose for 30 min		
	Monitor glucose for 30 min ²	Monitor glucose for 30 min ²	Repeat process after 20 min if the situation persists with the down arrow		
	Repeat process after 20 min if the situation persists with the down arrow	Repeat process after 20 min if the situation persists with the down arrow			

Risk in glycaemic control + ++ +++ 0

CH – Carbohydrates

1. When a trend arrow is not horizontal, and glucose is above 70 mg/dL, do not take action without repeating the reading twice with a 5 minutes interval. Adjust your approach according to the results.

2. Investigate the reason for the fall in glucose: Aerobic exercise? Is there still active insulin?

3. Investigate the reason for the rise in glucose: Insufficient or no insulin cover for a meal? Earlier meal rich in proteins and/or fats? Anaerobic exercise? Intensely stressful situation? The aim of this moment of reflection is to avoid repeating the situation.

4. If you are going to have a meal, subtract the 30 or 15 g of carbohydrates (depending on the case) in the calculation of mealtime insulin.

Table 2. Proposed therapeutic steps for users in response to glucose readings and trend arrows displayed on the FreeStyle Libre system (Abbott) when in a postprandial state, following the administration of bolus insulin.

POST-PRANDIAL TREND ARROWS WITH ACTIVE INSULIN ¹					
WHENEVER AN ARROW IS RISING OR FALLING, THE REASON FOR THE VARIATION SHOULD ALWAYS BE SOUGHT ^{2,3}					
GLUCOSE LEVELS (mg/dL) (the glucose values indicated should be personalized)	↓	↘	→	↗	↑
	Rapidly falling glucose (> 2 mg/dL/min)	Falling glucose (between 1 and 2 mg/dL/min)	Stable glucose (changing <1 mg/dL/min)	Rising glucose (between 1 and 2 mg/dL/min)	Rapidly rising glucose (> 2 mg/dL/min)
	Fall >60 mg/dL after 30 min	Fall 30–60 mg/dL after 30 min	Change <30 mg/dL after 30 min	Rise 30–60 mg/dL after 30 min	Rise >60 mg/dL after 30 min
GLUCOSE >180 mg/dL	Scan again after 30 min ²		Take a correction bolus if more than 2 hours have passed since the last insulin bolus, not including the active insulin If less than 2 hours have passed, do not take a corrective bolus Monitor glucose. If necessary, take a correction bolus when more than 2 hours have passed since the last insulin bolus	If more than 2 hours have passed since the mealtime insulin bolus, take a correction bolus based on the glucose value predicted by the arrow, not including the active insulin and aiming for the target glucose If less than 2 hours have passed, do not take a correction bolus Monitor glucose and, if necessary, take a correction bolus when more than 2 hours have passed since the last insulin bolus	If more than 2 hours have passed since the mealtime insulin bolus, take a correction bolus based on the glucose value predicted by the arrow, not including the active insulin and aiming for the target glucose If less than 2 hours have passed, do not take a correction bolus Monitor glucose and, if necessary, take a correction bolus when more than 2 hours have passed since the last insulin bolus
THERAPEUTIC TARGET 70–180 mg/dL	Have a meal with 30 g of CH without insulin if glucose is <130mg/dL ⁴ Monitor glucose for 30 min ² Repeat the procedure if necessary ²	Have a meal with 15 g of CH without insulin if glucose is <130 mg/dL ⁴ Monitor glucose for 30 min ² Repeat the procedure if necessary ²	Scan again at 30 min (you still have active insulin)	Repeat reading after 15 min. If the trend persists and more than 2 hours have passed since the last insulin bolus, take a correction bolus based on the glucose value predicted by the arrow, not including the active insulin and aiming for the target glucose ³	Repeat reading after 15 min. If the trend persists and more than 2 hours have passed since the last insulin bolus, take a correction bolus based on the glucose value predicted by the arrow, not including the active insulin and aiming for the target glucose ³
LOW GLUCOSE <70 mg/dL	Perform a fingerprick test Ingestion of 15 g of glucose if blood glucose <70 mg/dL Monitor glucose for 30 min ² Repeat process after 20 min if the situation persists with the down arrow When the glucose reaches 70 mg/dL, cover the active insulin with slow-absorption CH	Perform a fingerprick test Ingestion of 15g of glucose if blood glucose <70 mg/dL Monitor glucose for 30 min ² Repeat process after 20 min if the situation persists with the down arrow When the glucose reaches 70 mg/dL, cover the active insulin with slow-absorption CH	Perform a fingerprick test Ingest 15 g of glucose if blood glucose <54 mg/dL. If >54 mg/dL, ingest 10 g of CH Monitor glucose for 30 min When the glucose reaches 70 mg/dL, cover the active insulin with slow-absorption CH	Perform a fingerprick test Do not take glucose Monitor glucose for 60 min, with readings every 20 min Glucose is rising as a result of the approach taken, correction of hypoglycemia or dietary intake	Perform a fingerprick test Do not take glucose Monitor glucose for 60 min, with readings every 20 min Glucose is rising as a result of the approach taken, correction of hypoglycemia or dietary intake

Risk in glycaemic control + ++ +++ 0

CH – Carbohydrates

1. When a trend arrow is not horizontal, and glucose is above 70 mg/dL, do not take action without repeating the reading twice with a 5 minutes interval. Adjust your approach according to the results.

2. Investigate the reason for the fall in glucose: Aerobic exercise? Is there still active insulin?

3. Investigate the reason for the rise in glucose: Did you have a mealtime bolus? Did you adequately cover the CHs ingested? Did you take insulin 20 min before the meal? The aim of this moment of reflection is to avoid repeating the situation.

4. If you are going to have a meal, subtract the 30 or 15 g of carbohydrates (depending on the case) in the calculation of mealtime insulin.

cases the adjustments used were greater than the conservative approach recommended in the DirecNet guidelines.^{36,37}

Panel Recommendations

The panel considered that, given the absence of randomised clinical trials, there is no robust evidence that allows the formulation of a series of recommendations to be defined in this context.

Nonetheless, taking into account that: 1) because people with diabetes effectively use the information given by the trend arrows to adjust their insulin dose, there is a need for consensus on the matter in order to standardise clinical counselling; and 2), the trend arrows are an undeniable benefit of CGM systems that could, if properly used, improve the glycaemic control in people with diabetes; the panel has proposed a guide to therapeutic adjustment based on the interpretation of the trend arrows of the Freestyle Libre system and on the recommendations of Pettus and Edelman.³² It was decided that the level of glucose forecast 30 minutes after a reading (the average time for a rapid-acting insulin to start working) and applying the usual correction factor for each patient is a valid approach for using the trend arrows to calculate the correction bolus. It is important to stress that this proposal aims to generate initial guidelines. We recognise that these will be subject to alterations and revisions in line with the scientific evidence generated in the short and medium term by the ongoing accumulation of clinical data on this subject.

The panel also considered that: 1) the therapeutic adjustments will need to be tailored to the individual needs of each patient, their respective therapeutic target and the reason for adjustment (for example, the influence of meals and physical exercise); 2) therapeutic adjustment is a learning process for which clinical counselling is an important starting point: people wish to be and should be informed about the best way to manage their condition. It should be emphasised, however, that this is a continuous process, requires considerable education, and the results may not be immediate; 3) CGM enables verification of glucose levels following correction by repeat scanning, which is important to confirm if the effects are those expected and to reduce errors associated with any possible trend error inaccuracy; 4) taking into account the level of complexity of the calculations involved, patients should be informed that bolus calculators are essential tools to facilitate adjustment of the dose of insulin using the trend arrows and to avoid exposure to increase risk of hypoglycaemia by inappropriate correction of post prandial excursions; 5) patients should be warned of the danger of insulin stacking, so that any insulin still active in the body should be systematically subtracted from the new insulin bolus to be administered (for this purpose, and when properly scheduled, the computer programs available with insulin pumps and glucometers are a great help in calculating the most appropriate doses of insulin); and 6) trend arrow information becomes particularly relevant during low-glucose and evening periods to prevent hypoglycaemia.

Taking into account the above points, and in order to illustrate how the information obtained through the trend arrows should be incorporated into the therapy of the person with DM, [Tables 1 and 2](#) give guidelines on the measures to be taken before the different combinations of glucose values/trend arrows in the pre- or post-prandial periods (respectively).

Conclusion

The use of CGM systems, particularly the FreeStyle Libre flash glucose monitoring system, can lead to better glucose control in people with T1DM or T2DM who use insulin-based therapy,

through more personalised and rigorous clinical advice, as well as greater involvement and responsibility in the management of their condition. These systems incorporate the use of new parameters for the evaluation of glucose control – namely the ability to analyse several days' worth of glucose data, the detection of patterns of variation in glucose, and the use of trend arrows for adjusting insulin doses - as a complement to HbA1c levels. However, any new tool entails a learning curve. These recommendations aim to standardise clinical practice and communication with the patient in order to maximise the available data. Finally, the panel highlighted: the importance of evaluating the variability of glucose; the need to adapt therapeutic objectives to the specifics of each patient (specifically in terms of the limits of the target range and the time spent in this range); the importance of hypoglycaemia episodes and of recognising the patterns in the analysis of AGP and subsequent therapeutic adjustments; and the recognition of the potential of trend arrows and the need for more studies to validate the approaches proposed.

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