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Expert Opinion: Recommendation of diabetes experts on the use of FreeStyle Libre in diabetic patients in Poland

Introduction

The primary goal of diabetes treatment is to prevent the development of chronic complications of diabetes, which can be attained by, among other things, maintaining blood glucose values within the target range. Glycated hemoglobin (HbA_{1c}) is a commonly used risk marker for diabetes complications; however, this parameter has major limitations.

Hemoglobin A_{1c} value, reflecting blood glucose levels during the 3 months preceding the measurement, averages all episodes of hyperglycemia and hypoglycemia. This parameter does not reflect the variability of glycemia and does not provide precise information about the time spent in the target range of blood glucose. Patients with diabetes, especially those with type 1 diabetes, may experience considerable glycemic variability, with blood glucose levels changing rapidly from hyper- to hypoglycemia and vice versa.

Hypoglycemia not only causes acute neurovegetative and neuroglycopenic symptoms, but also is associ-

ated with the risk of falls, injuries, loss of consciousness or even death. In addition, it can lead to long-term consequences, which include cardiovascular events, and sometimes to episodes of depression. Rapid fluctuations in blood glucose are also associated with displacement of water in the body — dilution or increased concentration of fluids of various compartments and rapid changes in concentrations of substances other than glucose, which also carries a risk for the patient.

Current glucose monitoring has been integral part of adequate diabetes treatment for decades. Proper self-monitoring of blood glucose (SMBG) requires regular patient education in this regard, with particular emphasis on the frequency of blood glucose measurements and the interpretation of the results. Measured blood glucose values provide the basis for day-to-day modification of nutrition, physical exercise and insulin dose. Patients treated with multiple daily insulin injections or continuous subcutaneous insulin infusion (CSII) should perform a daily blood glucose profile, which means for many of them performing 10 or more measurements a day. These procedures are time-consuming, invasive, painful and causing discomfort in everyday life.

The FreeStyle Libre system is an excellent solution to these problems. It offers continuous glucose monitoring using a sensor-based technology to measure glucose level in interstitial fluid. When the patient scans the sensor to obtain glucose values, he or she simulta-

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neously receives a retrospective analysis of the glucose levels in the form of a continuous record. Information about the trends of glycemic variability presented by the device provides additional benefits related to improved effectiveness and safety of the therapy. Thanks to the possibility of generating an Ambulatory Glucose Profile (AGP), this system allows to precisely assess the level of metabolic control over the 90 days preceding the measurement, which corresponds to the period covered by HbA_{1c} value. The accuracy of the system allows for the current calculation of the HbA_{1c} value corresponding to the laboratory measurement of this parameter. This means that the useful, although imperfect, parameter which is HbA_{1c} can be monitored on an ongoing basis and integrated with the patient's SMBG.

Flash Glucose Monitoring

FreeStyle Libre is a Flash Glucose Monitoring (FGM) system. It is designed to measure glucose level in the interstitial fluid in patients with diabetes aged ≥ 4 years, also in pregnant women. It can also be used in other patients, without diabetes, who are at risk of glycemic disorders, e.g. in patients with prediabetes or recurrent hypoglycemia caused by hormonal or metabolic disorders.

The system consists of a reader, a device for wireless retrieval of data regarding glucose levels, and a sensor measuring the level of glucose in interstitial fluid of the subcutaneous tissue, which is worn on the skin.

The system converts the result of the measurement to the corresponding blood glucose value. It does not require user verification with blood glucose values.

Therapeutic benefits for patients

- The sensor continuously measures the glucose level for 14 days;
- Glucose monitoring without finger pricks translates in clinical practice into considerably more frequent measurements of glucose levels and more than 90% reduction in the number of blood glucose test strips (the IMPACT trial);
- The system does not require finger prick calibration;
- Computer software enables generating reports (glucose history), including AGP reports;
- Trend arrows indicates whether glucose level is increasing or decreasing and show trend dynamics, which significantly facilitates assessment of the risk of hypoglycemia in the next few hours (thanks to these data patients also learn how their body reacts, for example, to a specific diet or exercise; therefore, the system plays educational role as well);
- It is also possible to measure the level of glucose and ketones with the reader directly from the blood using test strips that are available and reimbursed in Poland;
- Readings can be obtained in a discreet way, through clothing. It is a comfortable solution, meeting the expectations of patients and their families — it allows for avoiding the violation of privacy and stigmatization of patients;
- Use of the system is easier and more convenient compared with test strips; therefore, it promotes more frequent measurements (more than 3-fold increase in the number of measurements performed) and improved glycemic control. Additionally, awakening the patients (e.g. a child) by a caregiver at night can be avoided;
- Full service for patients using FreeStyle Libre system (warranty/replacement, toll-free helpline).

Benefits demonstrated in clinical trials

Data from clinical trials indicate that the FreeStyle Libre system improves the effectiveness and safety of therapy in patients with type 1 and type 2 diabetes. It has been observed that the use of FreeStyle Libre decreased not only the number of hypo- and hyperglycemic episodes, but also reduced time spent in hypo- and hyperglycemia, including nocturnal episodes. It should be emphasized that hypoglycemia not only is a life-threatening condition (severe hypoglycemia) and decreases the patient's quality of life, but also is an important risk factor for the development of chronic, especially macroangiopathic, complications of diabetes. At the same time, the use of the FreeStyle Libre system resulted in extend time in the target glucose range, i.e. 70–180 mg/dL. Favorable changes were observed almost immediately after the readings from the device were opened to its users. Importantly, these changes were sustained and persisted for 6 months of follow-up (the IMPACT trial). The reduction of the time and number of hypoglycemic episodes has been achieved without insulin dose reduction or increase in HbA_{1c}. Extended time in normoglycemia with the reduction of the risk of hypo- and hyperglycemic episodes was also associated with a decrease in glycemic variability, a parameter now considered as an integral element in the evaluation of metabolic control of diabetes and an important prognostic factor for the development of diabetic complications. It is worth noting that glycemic variability is calculated automatically, similarly to the estimated HbA_{1c} (eHbA_{1c}), a parameter which in turn shows a far-reaching correlation with the biochemically determined HbA_{1c} value and can be obtained immediately after scanning FreeStyle Libre sensor without

having to waiting for a biochemical test result. The use of the FreeStyle Libre also allowed for a significant reduction in the number of test strips used, compared with using only the traditional method (a glucose meter). Several studies indicate that the FreeStyle Libre system provides glycemic monitoring that is accurate and consistent with the reference measurements for 14 days without the need to calibrate the device.

Surveys conducted among users have shown that patients appreciate the ease and convenience of measurements with the FreeStyle Libre system. It has been also observed that these patients more often follow the guidelines for glycemic monitoring than in the case of measurements performed using the conventional method. In the IMPACT trial, patients with type 1 diabetes using the FreeStyle Libre system measured glucose levels on average 15.1/day, which is much more often than in patients in the glucose meter group (5.6 measurements/day). The results of this survey and questionnaires assessing the quality of life also highlight the importance of the painlessness of measurements and a greater amount of information on glycemic variability, which allows patients to optimize their blood glucose levels. Ease of measurement and access to information also translated into clear preferences of patients, over 90% of whom declared that they prefer FreeStyle Libre rather than the traditional SMBG based on a glucose meter. Participants of the study also pointed to the increased awareness of the risk of hypoglycemia, security and privacy offered by the FGM device and the fact that it did not hinder usual daily-life activities, and even facilitated them by improving diabetes safety. The opinions of FreeStyle Libre users were similar regardless of the age of the respondents.

Patient register (Real World Data) — a confirmation of clinical data

Data from real-world medical practice confirm the above conclusions from clinical trials: the FreeStyle Libre system allows improving glycemic control. Particular attention is paid to the results of Dunn 2017 analysis, covering almost 51 thousand readers (about 280,000 sensors), indicating the relationship between the frequency of scans and the improvement in glycemic parameters. These results are all the more important because the frequency of scans in this analysis was even higher (an average of 16.3/day) than in the IMPACT study (an average of 15.1/day).

Interpretation of trends

Patients for whom the basis for glucose control is SMBG using a glucose meter make their therapeutic decisions based on the real-time but single blood glucose

value. Lack of information about the rate and direction of glycemic changes makes it difficult for patients to determine correctly the dose of insulin.

The FreeStyle Libre system provides two very important pieces of information beyond the current glucose level. The reader screen displays a graph showing the results of glycemia from the last 8 hours and trend arrows indicating the direction and rate of changes in the glycemic level. The patient should immediately modify his or her therapy taking into account this information.

In patients treated with functional intensive insulin therapy, modifications of therapy based on glycemic trends should include:

- change of meal-time and correction doses of insulin;
- intake of fast-acting carbohydrates or skipping a meal;
- considering physical activity.

Patients treated with personal insulin pumps may additionally modify the basal rate of insulin infusion and consider earlier replacement of infusion set.

Proper interpretation of trends by patients results in the reduction in the incidence of hypo- and hyperglycemia, decreased glycemic variability and improved time in target range. The use of glycemic trends should translate into a reduction in the incidence of acute diabetic complications and a reduction in the risk of development and progression of chronic diabetic complications. This information is also very useful for patients driving vehicles.

Considering all the above factors, patients should be educated on how to interpret glycemic trends. Currently, guidelines are being developed regarding proposed modifications of therapeutic decisions depending on the rate and direction of glycemic changes. The current interpretation of glycemic trends by patients will add a new dimension to diabetes self-control.

Ambulatory Glucose Profile: benefits for doctors

FreeStyle Libre enables performing systemic evaluation of the therapeutic process and treatment outcomes regarding blood glucose control in diabetic patients. FreeStyle Libre is the only system available on the Polish market which presents data using internationally recognized standardized approach to the analysis of glucose data — Ambulatory Glucose Profile (AGP) — both directly in the device and in the available computer software.

AGP provides a visualization of changes in glucose levels in the patient's averaged day of life. It is created on the basis of a daily chart summing up the results of glycemic measurements from many days or weeks

in one 24-hour chart. AGP shows averaged daily glycaemic variability for the 10th, 25th, 50th, 75th and 90th percentiles (the graph is generated with 5 percentile lines). Generated in this way and superimposed glucose curves show how often the glucose values are outside the target range (low or high values) and how often they fall within the target range. The visualization of the AGP reveals the tendencies to hypo- and hyperglycemia that could not be detected based on HbA_{1c} value. Scientific reports emphasize the need to prevent significant fluctuations of blood glucose, because it is considered as the most important factors contributing to the early onset of serious complications of diabetes. These goals cannot be achieved by assessing the level of glycaemic control using only HbA_{1c} monitoring, and AGP provides a very valuable supplement. Ambulatory glucose profile facilitates detecting hypo- and hyperglycaemic trends, which allows the identification of glycaemic patterns and proper patient education. Reports from clinical trials indicate that AGP has introduced an effective standard for analyzing glucose data and provides clinically relevant information about the patient's condition. The FreeStyle Libre[®] system due to its functionality (the device stores the reading every 15 minutes; it stores 90 days of glucose data) enables widespread use and practical application of the AGP protocols.

Summary of this section:

- a glucose graph and trend arrows showing blood glucose changes in the last few hours provide the basis for making therapeutic decisions;
- the system offers the analysis of standardized AGP, which enables:
 - identification of glycaemic patterns and adequate patient education (it helps patients to understand how daily activities impact blood glucose levels);
 - more detailed evaluation of the therapeutic process by the healthcare professionals.

New standard of glucose monitoring supplemented by SMBG

The FreeStyle Libre system, if it is permanently used by the patient, can replace the conventional glucose meter-based SMBG. This applies to patients with type 1 and type 2 diabetes treated with intensive insulin therapy except for the situations listed below.

In the following situations current readings from FreeStyle Libre should be verified with the finger prick test using a blood glucose meter:

- if hypoglycemia or impending hypoglycemia is reported by FreeStyle Libre;
- if the symptoms do not match the FreeStyle Libre system readings; symptoms that may be caused

by low or high blood glucose must never be ignored.

- during times of rapidly changing glucose levels when interstitial fluid glucose levels may not accurately reflect blood glucose levels; when blood glucose decreases rapidly, sensor reading may be higher than blood glucose level; and conversely, when blood glucose increases rapidly, sensor readings may be lower than blood glucose level.

Indication for use (patient groups)

FGM is indicated for use in the following groups of patients:

- patients with diabetes treated with intensive functional insulin therapy (multiple daily insulin injections, insulin pump therapy), regardless the type of diabetes;
- pregnant women with diabetes;
- patients with diabetes treated with conventional insulin therapy (2–3 injections daily), who are able to adjust insulin doses.

Other special groups of patients with an indication for the use of FGM:

- diabetic patients with the fear of needles or fear of hypoglycemia;
- patients with diabetes who drive the vehicles, leading an active lifestyle, working in shifts;
- patients with diabetes who require constant care (children, people with physical or mental disabilities);
- patients with diabetes and visual impairment or blindness (text-to-speech option)
- elderly patients with diabetes (FGM systems are easy to operate), also in senior care facilities and nursing homes.

Potential limitations of the system and their importance

FreeStyle Libre is similar in many respects to other interstitial-glucose-monitoring systems, but it also has some unique features. The FreeStyle Libre sensor is a transmitter that connects wirelessly to the reader; it does not have to be recharged and can be worn on the skin for 14 days.

Exceptionally high accuracy of measurements and trend indications without calibration as well as 14-day life span of a sensor are advantages obtained at the expense of limiting energy expenditure, resulting mainly from the lack of continuous transmission of data and audible alarms. On the other hand, this solution is simple from a technical point of view and can be easily integrated in the system as it is successively improved. Another feature simplifying the use of the

FreeStyle Libre system is FreeStyle LibreLink application which enables the caregivers to trace the patient's blood glucose readings and support the patient in daily diabetes control. This is particularly important for remote parental control over children with diabetes or for caregivers of elderly patients.

Noteworthy is the fact that glucose measurements are automatically registered every 15 minutes, which is less frequently than in continuous glucose monitoring (CGM) systems, but the time interval is similar to that of natural changes of glucose concentration in interstitial fluid (where the measurement is actually performed) in response to blood glucose fluctuations. This can also result in higher accuracy of the measurement and more reliable prognosis of glycemic changes (trend), because the device analyzes a 15-minute periods rather than, for example, 5-minute periods. In addition, this automatic registration does not exclude much more frequent measurements made by the patient by scanning the sensor, even every 1 minute, which is not possible when using CGM systems. Frequent (every few minutes) monitoring of glucose levels may be useful in special situations.

There is only one site for administration of the FreeStyle Libre sensor recommended by Abbott — on the back of the arm. This is important for optimal accuracy of measurements, because this location was associated with the best results in manufacturer's quality tests. On the one hand, this can be considered as a limitation, although the use of sensors inserted subcutaneously do not cause significant tissue injury and therefore the limitation of rotation areas, even for smaller children, is not a problem. On the other hand, placing sensor within previously examined areas of the body, with known characteristics of vascularization and involvement in the glycemic balance, results in greater accuracy and repeatability of measurement results. If the user, in spite of Abbott's suggestions, places the sensor in another area for important reasons, the sensor will still work, although more frequent verifications of obtained readings with the result of the glucose meter measurements are required, especially in the case of abnormal blood glucose values.

FreeStyle Libre also stands out from other CGM systems due to its flat sensors with rounded edges, well-fitting to the body. Thanks to all these features the sensor is better secured on the skin and less susceptible to accidental detachment when, for example, caught by clothes, etc.

The biggest limitation preventing the widespread use of the system is the lack of reimbursement for patients, which limits its availability. The reimbursement would be, at least partially, offset by reducing the

cost of test strips for glucose meters. The example of patients already using FreeStyle Libre shows that the use of strips for glucometers decreases about 10 times. They are not needed for FreeStyle Libre calibration, and are used, along with reader's indications, only in the specific situations listed above. Moreover, the Libre reader not only can be used as a glucometer using glucose strips (Optium Xido), but also can measure ketones (β -hydroxybutyric acid) in the blood (Optium Xido β -ketone strips), which allows determination of significant hazards for the patient. In addition, there is still a need to improve diabetes control and reduce the costs resulting from the development of complications and acute, transient, often life-threatening conditions (costs of outpatient visits and hospitalizations). Currently in Poland, the reimbursement of CGM systems is limited to type 1 diabetes patients in a specific age range who are users of personal insulin pumps. It also requires meeting additional criteria related to diabetes control. These conditions discriminate against patients with type 1 diabetes who have poor metabolic control or do not have (for various reasons) a personal insulin pump. They also discriminate against patients with type 2 diabetes treated with insulin, usually injected with pens. It should be remembered that many patients with type 2 diabetes are also treated intensively with insulin and they also require continuous monitoring of therapy.

Software

Since the second half of 2018, patients using FreeStyle Libre in Poland can use innovative digital solutions: FreeStyle LibreLink and LibreLinkUp applications available on Android and iOS systems as well as the LibreView system allowing for comprehensive data analysis and on-line access to glucose data.

Below are the features of these applications and the system:

The **FreeStyle LibreLink application** allows users of the FreeStyle Libre system to scan the sensor using a smartphone, providing greater convenience and discretion. It also allows the patient to reduce the cost of blood glucose monitoring, because there is no need to use a separate reader to monitor glucose.

The benefits for patients resulting from using this application:

- patients can use FreeStyle LibreLink on their smartphone instead of or simultaneously with the FreeStyle Libre reader;
- rich patient interface is available from a large high-resolution touch screen;
- patients can easily add notes to track meals, insulin doses, exercise and other events;

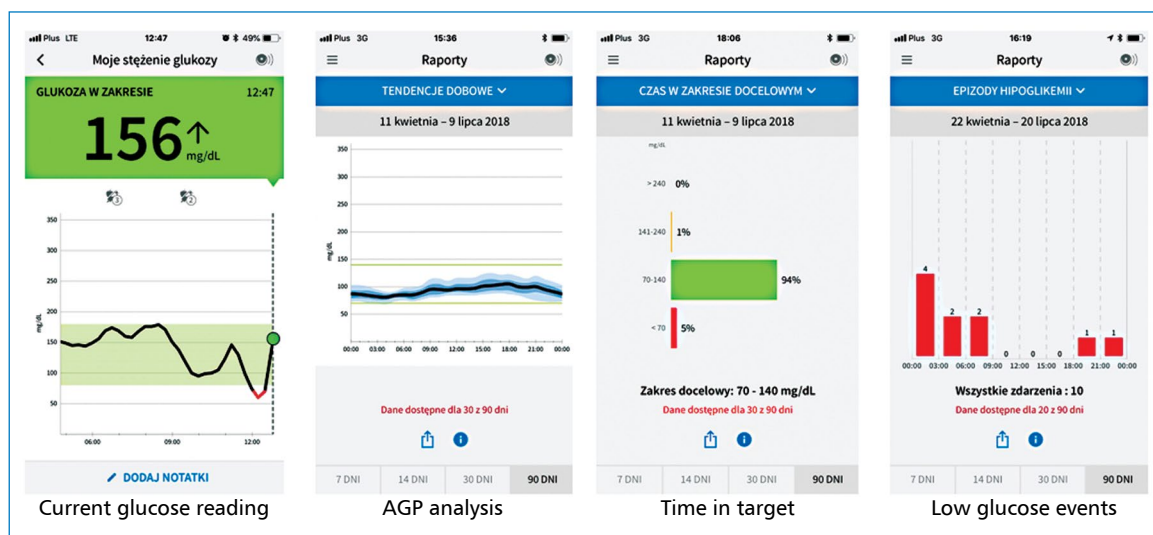


Figure 1. Some examples of reports available to the patient using the FreeStyle LibreLink application

- cooperation of FreeStyle LibreLink with LibreLinkUp enables connection with caregivers;
- text-to-speech option converts glucose readings into spoken audio, which is important for users who are blind or have impaired vision.

Some examples of reports available to the patient using the FreeStyle LibreLink application are presented in Figure 1.

LibreLinkUp is a mobile application that allows parents and caregivers to remotely monitor glucose readings in patients who scan the sensor using the FreeStyle LibreLink application.

Figure 2 shows an example screenshot from a smartphone used by a caregiver working with the FreeStyle LibreLinkUp application.

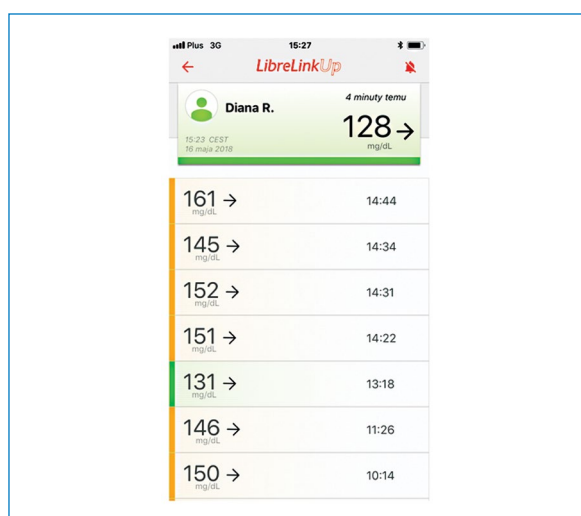


Figure 2. Example screen available to a caregiver using the LibreLinkUp application

LibreView is a cloud-based diabetes control system offered by Abbott and Newyu, Inc. LibreView provides a secure data repository for the FreeStyle LibreLink application and enables easy sharing of glycemic data with health care professionals or other people. The data is automatically sent to the LibreView system when the phone is connected to the Internet.

The main benefits of using this system are:

- glucose data can be simply uploaded from the reader via a computer and accessed from anywhere from any internet-connected device;
- the glucose data of patients using FreeStyle LibreLink application will be automatically transferred to their LibreView account each time the FreeStyle Libre sensor is scanned;
- clear, easy-to-read reports which allow the patient to discover glucose patterns and trends immediately;
- optimization of treatment plans thanks to remote patients monitoring and cooperation with a healthcare team.

Using the above-described applications and the system allows for remote control of glycemia with tools perfectly matching the concept of telemedicine, which not only significantly increases patient safety, but also reduces direct and indirect expenses by the public payer. Additionally, this technology provides real-world data showing actual effects of the use of a specific medical technology.

Education

Type 1 diabetes results from destruction of pancreatic beta cells. These cells are the source of insulin and a perfect natural regulator of its presence and access

to all cells in various organs. The beta cells precisely regulate insulin secretion according to the changing needs of the body. During the initial stage of type 2 diabetes, beta cells produce insulin in excessive amount. The progression of the disease is characterized by a disturbed profile of and a progressive decrease in insulin secretion. Thus, in the treatment of both type 1 and type 2 diabetes, it is necessary not only to supplement insulin, but also replace the lost regulatory function of the beta cells.

The way to improve this situation is proper education of the patients and/or their caregivers so that they understand the role of insulin and can predict the effects of its administration, in particular in relation to meals and physical exercise. It is also important to anticipate a change in insulin requirements during additional illness or in special situations. A particular difficulty in good diabetes therapy is associated with individual differences in the course of the disease and various life situations.

In practice this means that diabetes education, which is an integral part of the treatment of a patient with diabetes, must also be individualized. The patients actively participate in treatment, because they ultimately make therapeutic decisions. Their task is to observe their bodily reactions to meals, physical activity and, finally, insulin dosing, and sometimes also effects of other drugs influencing glycemia. These observations as well as drawing conclusions from them and constant modification of the therapy are based largely on glucose monitoring. The patient has to verify the recommendations received from the therapeutic team in real life, which is done by assessing the glycemic effects of the therapy. In healthy people, pancreatic beta-cells control glycemia and constantly regulate insulin secretion. In diabetes, FreeStyle Libre allows the user to imitate the natural mechanism of glycemic control. Indeed, it supports the patient's therapeutic decisions. FreeStyle Libre, by displaying real-time glycemic values, indicating the anticipated glycemic trends, storing these data in memory and offering the possibility of reviewing data from the past few hours, 24 hours or many days allows the patient to successively adjust his or her self-management and constantly improve glycemic control. This applies to evaluation of the risk of hypo- and hyperglycemia episodes, their amplitude and timing, identification of repeating patterns of normal and abnormal blood glucose values.

Patient self-education activity aiming at expanding their knowledge about diabetes is also needed. It involves arranging situations that are associated with

changes in insulin dosing, diet or physical activity in order to carefully observe glycemic effects and evaluate the sensitivity to insulin, calculate insulin/carbohydrate ratio, assess the hypoglycemic effect of exercise etc. Thanks to the FreeStyle Libre system, diabetic patients can easily track glycemic changes even in very narrow time intervals, store them in the system's memory, and then draw conclusions about modifications or continuation of therapy i.e. insulin dosing, diet and physical activity.

The FreeStyle Libre system also allows the calculation of the corresponding HbA_{1c} value based on numerous glucose readings recorded by the sensor; its high accuracy has been confirmed by laboratory tests. The educational value of this efficient HbA_{1c} calculation is to indicate whether the therapeutic goal expressed by this parameter is achieved. It allows the patient to understand the relationship between the calculated HbA_{1c} value and his or her glucose profile — its amplitude, episodes of hypo- and hyperglycemia, etc. This makes the interpretation of HbA_{1c} parameter more valuable and informed.

Summary

On the basis of clinical trials, scientific evidence and experience from everyday practice, the use of FreeStyle Libre is recommended as a glucose monitoring system in patients with type 1 and type 2 diabetes treated with intensive insulin therapy. FreeStyle Libre supports treatment and can contribute to:

- improvement in diabetes control by decreasing mean blood glucose levels and HbA_{1c};
- reduction of the number of hypoglycemic episodes and time spent in hypoglycemia; it is particularly relevant to patients with frequent hypoglycemic episodes and hypoglycemia unawareness;
- reduced glycemic variability;
- potential decrease in long-term complications of diabetes;
- improved patient quality of life and safety.

We express the opinion that the FreeStyle Libre system should be widely available, also taking into account its affordability, for Polish patients with type 1 and type 2 diabetes treated with intensive insulin therapy.

The Expert Group was established by Abbott Laboratories Polska to express the above opinion as part of the meeting of the Advisory Committee, which was held in Warsaw on November 21, 2017 and on March 23, 2018.

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