REVIEW PAPER

Real-time continuous glucose monitoring systems in patients with type 1 diabetes. Expert group report

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ABSTRACT

The beginning of the 21st century saw the arrival of continuous glucose monitoring systems (CGMS). For over a decade they were seen as an excellent tool providing data on the daily glucose profile patterns in patients with diabetes, but confined to research. Over 20 years ago hardly anyone expected CGMS to become an extremely useful device in everyday life with diabetes as the cost, the burdensome design and accuracy were at the time the main concerns. However, in the last few years CGMS has become available to the entire diabetic population, and it is affordable to many of them. During this time, the technology developed immensely, and patients can now use reliable systems to give them instant, online insight into their blood glucose excursions 24/7. Moreover, the accumulated evidence indicates that arming patients with knowledge of their current glucose value and the trends of its variability translates into significant improvement in overall glucose management. The patients who benefit most, as research data and clinical experience show, are those who are treated with insulin, in particular individuals with type 1 diabetes. Progress in glucose monitoring – the journey from measuring urine glucose through portable glucose meters to CGMS – has also changed the metrics that are used to assess metabolic control of diabetes. In recent years the concept of time in range (TIR) has been introduced, which is now being widely adopted into clinical guidelines and practice. In 2021 the use of real-time CMGS in patients with type 1 diabetes was recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) as a main tool for self-monitoring of blood glucose. The article is a state-of-the-art review presenting current evidence-based knowledge and views on the practical use of CGMS in this group of patients, with clinical implications and opportunities discussed in detail.

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Introduction

Type 1 diabetes mellitus results from the body losing its ability to produce insulin, the hormone responsible for energy uptake into the cells, delivered primarily in the form of glucose. Treatment of type 1 diabetes is based on administering exogenous insulin either by multiple injections or by continuous subcutaneous infusion using a personal insulin pump.

Insulin was discovered approximately 100 years ago, but the reproduction of its physiological activity profile still remains a challenge. In fact, it is a hormone that is potent but at the same time also very precise in its action and even a slight excess in insulin over the body's requirements may cause hypoglycaemia. Conversely, a slight deficiency of this hormone leads to a significant increase in the blood glucose level. As evidenced by research studies, both hypoglycaemia and hyperglycaemia cause damage to many organs and systems by destroying blood vessels and peripheral nerves, making diabetic patients disabled or even causing them to die prematurely.

In fact, how should the patient know how much insulin to take, for example before lunch? The patient obtains this information on the basis of the result of measurement of the blood glucose level and knowledge on the quantity of insulin that is necessary to control glycaemia in the case of the specific meal, taking into account its qualitative composition and energy value. The appearance of glucose meters over 40 years ago made it possible for patients to check their blood glucose levels several times during the day, but the real breakthrough was the introduction of continuous glucose monitoring (CGM) systems at the turn of the 21st century. In fact, a glucose meter enables the patient to determine the glucose level at a specific time and only when the patient performs the measurement (and this usually occurs no more than 6–10 times a day). In contrast, CGM provides continuous information about the current glucose levels and their trends (whether the glycaemic profile is rising or falling), and also warns the patient about impending hypoglycaemia or marked hyperglycaemia. In the most advanced models of personal insulin pumps with integrated CGM, insulin administration is automatically stopped temporarily when blood glucose is falling and resumes when blood glucose increases to a safe level. To understand the significance of CGM for blood glucose control in comparison with the role of glucose meters, diabetes treatment may be compared with driving a car. The use of a glucose meter opens the patient's (driver's) eyes in relation to blood glucose levels several times a day, and the use of CGM, in particular real-time continuous glucose monitoring (rtCGM), means that the patients (driver) have their eyes open all the time. Therefore, patients can see their continuous glycaemic profile all the time, e.g. on the display on their pump or phone, and can thus predict how their body will react to an upcoming meal, physical exercise or insulin dose. How can you safely drive a car (control diabetes) when you only open your eyes a few times during your drive? It is impossible. You have to keep your eyes open at all times to safely reach your destination (treat your diabetes so that no hypoglycaemic and no marked hyperglycaemic episodes occur). This is the purpose for which CGM has been designed.

Importance of optimisation of metabolic control for the prevention of micro- and macrovascular complications of type 1 diabetes

In accordance with clinical guidelines, metabolic control of diabetes is obtained when the patient achieves the target blood glucose level (glycaemia value), blood lipid levels and blood pressure values. Poor glycaemic control manifests as chronic hyperglycaemia, high daily blood glucose fluctuations, and frequent episodes of hypoglycaemia, leading to cell and organ dysfunction and pathological changes in their structure. The cells to which glucose is transported in a non-insulin-dependent manner are particularly vulnerable to glycaemic dysregulation. They include endothelial cells and nerve cells.

Neurovascular complications of diabetes (microangiopathy, macroangiopathy, neuropathy) are clinically manifested as retinopathy and diabetic maculopathy, chronic diabetic kidney disease and diabetic neuropathy. Pathology of small vessels and microcirculation (microangiopathy) also contributes to the development of periodontal disorders, heart failure and the pattern of atherosclerosis which is characteristic for diabetes. Experimental studies and randomised clinical studies indicate that optimisation of blood glucose control reduces the risk of development and progression of chronic neurovascular complications of diabetes.

The key study investigating the treatment of type 1 diabetes that provided evidence for

the benefits of intensive insulin therapy and improved glycaemic control is the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC). The interventional part of the study (DCCT) demonstrated that, in comparison with conventional treatment, intensive insulin therapy based on the basal-bolus regimen, aiming for preprandial blood glucose levels of 70–120 mg/dl and postprandial glucose levels of < 180 mg/dl, makes it possible to achieve significantly lower glycated haemoglobin (HbA_{1c}) values. Glycated haemoglobin is a measure of average glucose levels and lower values of it were associated with a lower risk of microvascular complications within a relatively short period of 6.5 years. Diabetes Control and Complications Trial results published in 1993 provided a benchmark for target HbA_{1c} values in patients with diabetes. Defining the treatment target of $HbA_{1c} \leq 7\%$ was based on the reduction of the risk of development and progression of microangiopathic complications characteristic for diabetes that was found when such values were maintained. Improved blood glucose control and stable HbA_{1c} values of approximately 7% for 6.5 years of the duration of the DCCT yielded positive changes in the long term. In comparison with the conventionally treated group, a significantly lower cardiovascular risk (reduction of cardiovascular events by as much as 47%) was already noted after 17 years in the group receiving intensive treatment, and a 32% reduction in the risk of a major cardiovascular event (stroke, non-fatal myocardial infarction and also death due to other cardiovascular causes) was found after 30 years. In the DCCT, long-term variability of HbA_{1c} measured based on the standard deviation was associated with the development of chronic complications of diabetes.

Continuous glucose monitoring makes it possible to precisely determine its short-term variability. There is scientific evidence indicating that high daily fluctuations in glycaemia contribute to the development and progression of neurovascular complications. The application of CGM systems, especially in insulin therapy, using a personal insulin pump, particularly in the closed loop algorithm, is a solution that optimises blood glucose control. Owing to such solutions, it is possible to obtain normal glucose levels (normoglycaemia), with regard to both mean values and blood glucose variability, in patients with type 1 diabetes. More time spent in normoglycaemia constitutes an opportunity for a longer life without diabetic complications [1–5].

Prevention of hypoglycaemia as one of the priorities in diabetes treatment

Hypoglycaemia, i.e. low blood glucose levels, is defined as lowering of the blood glucose level to below 70 mg/dl. This is one of the most dangerous side effects of diabetes treatment, especially of insulin therapy. In patients with diabetes, hypoglycaemia frequently constitutes a barrier to obtaining good metabolic control, because many patients maintain their glucose levels too high out of concern that this may occur. Recurrent hypoglycaemic episodes, even minor episodes, reduce quality of life and interfere with the normal functioning of the patient at school, at work and in the family.

There are large discrepancies in the estimated incidence of hypoglycaemia; however, data from a number of publications indicate that hypoglycaemic episodes occur in up to more than half of diabetic patients. The clinical presentation of hypoglycaemia can vary and may depend on the duration of diabetes and the patient's age, diabetic complications and comorbidities. Patients describe their hypoglycaemic symptoms differently. Such symptoms may differ (even in the same person), depending on the time of occurrence (during the day or at night) or the rate of decrease in blood glucose levels. The most common symptoms of hypoglycaemia include:

- neurovegetative symptoms: hunger, headache, increased sweating, tremor, paleness, anxiety, irritability, palpitations;
- neurological symptoms: sensory and visual disorders, impaired concentration, transient paresis and hyporeflexia through to seizures, coma, lack of reaction to stimuli and areflexia;
- psychiatric symptoms: abnormal behaviour (sometimes resembling symptoms of alcohol intoxication), depressive states, agitation, hallucinations, slurred speech.

An exceptional clinical situation is when the patient does not perceive the typical warning symptoms of hypoglycaemia, i.e. the so called unawareness of hypoglycaemia, which is one of the causes of recurrent severe hypoglycaemic episodes with loss of consciousness. This phenomenon is particularly common in patients who have lived with type 1 diabetes for many years. It occurs in approximately 15–20% of individuals in this group.

A very important issue in the treatment of patients with type 1 diabetes is nocturnal hypoglycaemia, which does not cause the patient to wake up in most cases. Nocturnal hypoglycaemia may be suspected in a situation when the patient experiences increased sweating or nightmares while sleeping or has headaches after waking up. Because nocturnal hypoglycaemia is a source of anxiety for many insulin-treated individuals, patients often eat some snacks before going to sleep in an attempt to avoid it, which causes hyperglycaemia (high glucose levels) during the night and early in the morning. A recurrence of such situations may lead to impaired metabolic control of diabetes and an increased risk of development of chronic complications of the disease. Furthermore, other negative consequences of nocturnal hypoglycaemia are worth noting, such as poor sleep quality, fatigue or impaired functioning during the day. The consequences also include absenteeism at work, the need to perform additional blood glucose measurements on the day after nocturnal hypoglycaemia, the fear of recurrence of hypoglycaemia, and reducing the insulin doses recommended by the physician, which is not always justified. In extreme cases, nocturnal hypoglycaemia may lead to the patient's death.

Until not so long ago, the only measurement method available for patients in the diagnostics of hypoglycaemia, similar to daily self-monitoring of diabetes, was the invasive measurement of glucose levels in capillary blood (collected from the fingertip) using a glucose meter. In recent years, the method of CGM within the interstitial fluid has gained popularity in diabetes monitoring. Continuous glucose monitoring systems make it possible to improve the metabolic control of diabetes and to reduce the risk of hypoglycaemia, simultaneously improving quality of life for the patients. Particularly good treatment results with regard to both diabetes control and treatment safety can be obtained when using CGM systems integrated into a personal insulin pump. In these devices, insulin infusion may be automatically stopped at a low glucose level or if there is a risk of hypoglycaemia. The possibility of using such systems is of great importance, especially for patients with hypoglycaemia unawareness and for the prevention of nocturnal hypoglycaemia. Since the development of technologically advanced tools in modern diabetology aims to improve such devices further, systems integrating CGM with an insulin pump are currently undergoing intensive clinical trials. The purpose of these trials is to develop a fully automated insulin administration system, called a "closed loop" system [6, 7].

Continuous glucose monitoring: definitions, clinical utility, available measurement technologies

With each year of the past decade, CGM systems have become more and more popular. They measure glucose concentrations in the interstitial fluid in a continuous manner, significantly reducing the invasiveness of blood glucose measurements and providing far more information than measurements performed using glucose meters. These devices provide information about the current glucose level and the short-term dynamics of its changes, as well as illustrating its course round the clock. The patient receives the result of the current measurements, trend signalling and retrospective analysis of glucose levels, presented as a continuous trace. This is beneficial for self-care/self-monitoring of diabetes by the patient because it leads to an understanding of the relationship between daily life events and changes in glucose levels, and improves the effectiveness and safety of the therapy. Furthermore, for members of the diabetes treatment team, these systems are helpful for precise evaluation of the patient's glycaemic control level, for example, over the past 90 days, where glycaemic levels are reflected by HbA_{1c}. The systems are sufficiently accurate to enable an ongoing estimation of the parameter that corresponds to laboratory measurements of HbA_{1c} and variation in blood glucose levels. The use of CGM systems enables a more precise definition of blood glucose control parameters, such as mean blood glucose level, blood glucose variability, time in range (TIR) of target glucose levels and determination of target glucose values in diabetes therapy.

The sensor in a CGM system is responsible for continuous measurement of glucose concentration in the interstitial fluid, and it determines both blood glucose levels and the dynamics of their continuous changes based on the defined algorithms. The range of available CGM systems is being continuously expanded, with the introduction of new or updated algorithms. Their accuracy is improving and approaching the accuracy of glucose meters, without any calibration being required. The receivers for glucose level recordings in CGM systems are often smartphones and, in the case of integrated systems, the CGM trace

is visible on the display on the personal insulin pump.

As part of the development of CGM systems, a secure data sharing model has also been introduced. This allows third parties to access the data, with the consent of the user. Using the Internet, individuals close to the patient – defined as "therapy partners" (e.g. parents) – may remotely observe blood glucose changes in real time (e.g. in their child) on mobile apps or on the software manufacturer's website. This function is available, for example, in the Guardian Connect, Dexcom G5 and G6 systems. An interesting option in the Guardian Connect system is also the automatic sending of text messages to treatment partners, e.g. information about changes in blood glucose levels. Internet connectivity also enables the rapid transfer of data from the CGM system applications to an Internet cloud, which is used, for example, in telemedicine. Another result of CGM development is its integration into insulin pumps. An example is the MiniMed 780G system, which automatically adjusts insulin delivery and corrects high blood glucose values, thanks to the development of rtCGM algorithms and improved measurement accuracy.

Continuous glucose monitoring systems are based on one of two main principles:

- rtCGM;
- intermittently scanned continuous glucose monitoring (isCGM), where the measurement is performed by scanning (FreeStyle Libre, i.e. flash glucose monitoring, an isCGM-flash glucose monitoring [FGM] system).

In view of the sensor type and blood glucose measurement method, CGM systems are classified as those using:

- transdermal sensors with an enzymatic measurement method (rtCGM and isCGM-FGM systems);
- long-term sensors implanted under the skin, using a fluorescence-based measurement method (Eversense XL).

Table 1 provides a comparison of the main characteristics of blood glucose monitoring systems that are available for patients.

Owing to the differences between the individual modern blood glucose monitoring systems, the patients may select the system that will best satisfy their expectations in collaboration with their diabetes treatment team (Table 2). For patients with hypoglycaemia unawareness or with recurrent serious hypoglycaemic episodes, rtCGM or isCGM-FGM2 systems with alarms (isCGM-FGM2, i.e. FreeStyle Libre 2) are recommended, preferably with low blood glucose prediction.

Standards of glycaemic control assessments based on continuous glucose monitoring traces and international consensus on the time in range

From the 1980s, daily glycaemic control in patients with type 1 diabetes was based on measurements of blood glucose levels (glycaemia) in capillary blood performed by the patient at home using a glucose meter. However, even when performed in line with the guidelines of scientific societies, at least 6 times a day, the measurements do not reflect glucose levels in a comprehensive manner. The values averaged for 14, 30 or 90 days, recorded in the glucose meter memory, give only a random sample-based representation of glucose levels measured at specified times of the day. Therefore, HbA_{1c}, reflecting average blood glucose levels over the past 2–3 months, has remained the most important parameter used for the assessment of long-term blood glucose control. However, HbA_{1c} is not an ideal parameter as, for example, personal factors (e.g. certain types of anaemia and inter-individual differences in the intensity of glycation reactions) may interfere with the reliable interpretation of its result and it does not reflect the daily fluctuations of blood glucose levels or the frequency of hypoglycaemia.

Continuous glucose monitoring systems assess glucose levels in the interstitial fluid many times an hour and enable the collection of information on these measurements for any length of time (days, weeks, months, and even years), and thus are substantially devoid of the above limitations. Their widespread use in clinical practice and results from reliable studies provided the basis for the development of the International Consensus on Time in Range, i.e. the recommendations describing the interpretation and method of analysis of records from CGM (rtCGM, or intermittently scanned CGM-flash glucose monitoring – isCGM-FGM) devices. These recommendations define the formal conditions of CGM records and also the elements which should be included in the report on CGM analysis and how to interpret this report. A reliable report should include the analysis of 14 or more days on which CGM was active for at least 70% of the time. One of the most important parameters of blood glucose control included in the re-

Table 1. Comparison of blood glucose measurement methods: glucose meters, intermittently scanned continuous glucose monitoring-flash glucose monitoring and real-time continuous glucose monitoring*

Variable	Glucose meter	isCGM-FGM	rtCGM
Body fluid in which glucose concentration is measured	Capillary blood	Interstitial fluid	Interstitial fluid
Approval – patient's age	No age limit	From 4 years of age	Medtronic systems: no age limit Dexcom: from 2 years of age Eversense XL: from 18 years of age
Approval for use in pregnancy	Yes	Yes	Medtronic systems: yes Dexcom: yes Eversense XL: no
Invasiveness of measurement	Pricking of fingertip (or alternatively the earlobe) for each measurement	Sensor placement every 14 days	Sensor replacement Medtronic: every 6 or 7 days Dexcom: every 7 or 10 days Eversense XL: every 180 days
Need to calibrate with a glucose meter	Not applicable	No	Yes – minimum twice daily Dexcom G6: no
Accuracy	Requirement of meeting the EN ISO 15197: 2015 Standard: 95% of results with an error not exceeding ±15 mg/dl for glucose concentrations < 100 mg/dl or ±15% for glucose concentrations ≥ 100 mg/dl	MARD: 9.0%	MARD Medtronic, Guardian Connect + Enlite: 9.1% Guardian Sensor 3: 8.7% (placed on the arm, 2–3 calibrations daily) Guardian Sensor 3: 9.1% (placed on the arm, 2 calibrations daily) Dexcom G5, G6: 9% Eversense XL: 9%
Number of measurements/ recordings per day	Depends on the requirements and preferences of the patient (at least 4× daily with intensive insulin therapy; optimally at least 8× daily)	Recording of results every 15 min (96 measurements per day); requirement to scan no less frequently than every 8 hours to obtain the full 24-hour trace	Recording of results every 5 min (288 measurements per day); requirement to calibrate with a glucose meter no less frequently than every 12 hours to obtain the full 24-hour trace (except for Dexcom G6)
Information on trends in blood glucose changes	No	Yes	Yes
Warning alarms	No	No	Yes
Possibility to take treatment decisions (in particular on insulin dosage) on the basis of the measurement performed with the device	Yes	Yes	Systems: MiniMed Veo: no MiniMed 640G: no MiniMed 670G: no MiniMed 780G: yes MiniMed 720G: no Dexcom G4: no Dexcom G5, G6: yes Eversense XL: no

isCGM-FGM – intermittently scanned continuous glucose monitoring flash glucose monitoring, rtCGM – real-time continuous glucose monitoring

**Adapted from the user manuals for the individual systems/devices and information materials provided by the manufacturers; intermittently scanned continuous glucose monitoring-flash glucose monitoring (i.e. FreeStyle Libre manufactured by Abbott Diabetes Care Inc.). Medtronic systems: MiniMed Veo, MiniMed 640G, 670G, 780G, 720G, Guardian Connect; Dexcom systems: G5, G6; Senseonics system: Eversense XL; MARD – mean absolute relative difference.*

Table 2. Overview of the available advanced real-time continuous glucose monitoring systems*

Manufacturer of the rtCGM system	Medtronic	Dexcom	Senseonics
Devices	Guardian Connect (mobile device) CGM coupled with insulin pumps: MiniMed Veo, MiniMed 640G, MiniMed 670G MiniMed 780G, MiniMed 720G	Dexcom G4 PLATINUM Dexcom G5 Mobile Dexcom G6	Eversense XL
Sensors	Transdermal	Transdermal	Implanted under the skin
Placement site	Recommended sites: abdomen and upper portion of buttocks	Children: abdomen and upper portion of buttocks, posterior part of upper arm	Upper arms
	Posterior part of upper arm (Guardian Sensor 3), but placement is possible at any site with sufficient subcutaneous tissue	Adults: abdomen (Dexcom G5), abdomen, posterior part of upper arm (Dexcom G6)	
Level of difficulty of sensor placement	Moderate	Dexcom G5: fairly simple/moderate Dexcom G6: simple	Sensor placed by a physician
Sensor replacement frequency	Enlite sensor: every 6 days Guardian Sensor 3: every 7 days	Dexcom G4 and G5 sensors: every 7 days Dexcom G6 sensor: every 10 days	Every 180 days
Transmitter	Replacement every 12 months	Dexcom G4: replacement every 6 months; Dexcom G5 and G6: replacement every 3 months	Replacement every 12 months
Data storage in the transmitter	Guardian Connect: up to 10 hours MiniMed Veo: up to 40 minutes MiniMed 640G MiniMed 670G MiniMed 720G MiniMed 780G: up to 10 hours	Dexcom G5 and G6: up to 3 hours in the transmitter	Up to 90 days
Receiver	Guardian Connect: mobile device with the Guardian Connect application: in coupled systems – insulin pumps In the MiniMed 780G system: added application for the system user and a dedicated application for Therapy Partners	Dexcom G4: dedicated receiver Dexcom G5: dedicated receiver or mobile device with the Dexcom G5 Mobile application Dexcom G6: dedicated receiver or mobile device with the Dexcom G6 application Dexcom follow application for Therapy Partners with the option of setting separate alarms	Mobile device with the Eversense application
Wireless range	Guardian Connect: 6 m; systems coupled with an insulin pump: 1.8 m MiniMed 720G, MiniMed 780G: Bluetooth connectivity (BLE)	6 m	7.6 m

Table 2. Cont.

Manufacturer of the rtCGM system	Medtronic	Dexcom	Senseonics
Information on trends	MiniMed Veo: 5 ranges Guardian Connect, MiniMed 640G	7 ranges	5 ranges
	MiniMed 670G MiniMed 720G MiniMed 780G: 7 ranges		
Alarms for low and high blood glucose levels	Yes	Yes	Yes
Predictive alarms	Yes	Yes	Yes
Blood glucose trend alarms	Yes	Yes	Yes
Vibration alarms for low and high blood glucose levels and blood glucose trends from the transmitter without a receiver	No	No	Yes
Device calibration	Minimum twice daily	Dexcom G4, G5: twice daily Dexcom G6: not required	Twice daily
Option of sending data to an Internet cloud	Guardian Connect MiniMed 720G MiniMed 780G: yes (when connected to the Internet, continuous data sending to therapy partners) MiniMed Veo MiniMed 640G MiniMed 670G: there is no continuous data sending; data from the pump memory for the given period are sent with the use of the CareLink Personal software	Yes (when connected to the Internet, continuous data sending to therapy partners from Dexcom Follow and to the Dexcom Clarity data analysis system)	Yes (when connected to the Internet, continuous data sending)

CGM – continuous glucose monitoring, rtCGM – real-time continuous glucose monitoring

**Adapted from the user manuals for the individual systems and information materials provided by the manufacturers.*

Table 3. Target values for blood glucose control parameters in patients with diabetes using continuous glucose monitoring (real-time continuous glucose monitoring/intermittently scanned continuous glucose monitoring-flash glucose monitoring). The target ranges are presented for glucose levels, the recommended ranges for the time spent with blood glucose levels within the target range (time in range), the time spent with blood glucose levels below the target range (time below range) and for the time spent with blood glucose levels above the target range (time above range) [8]

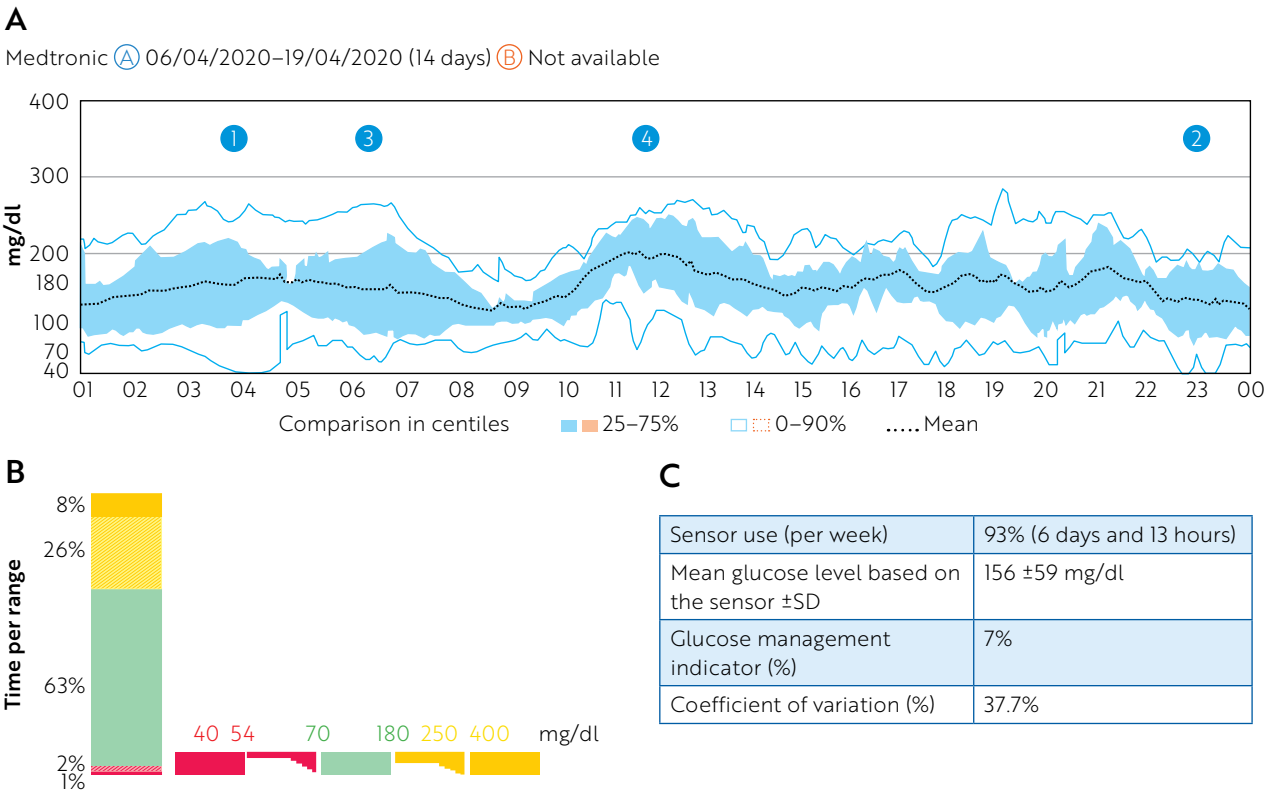
Patient group	Time in range		Time below range		Time above range	
	% of readings (time during the day)	Target range	% of readings (time during the day)	Blood glucose levels below the target	% of readings (time during the day)	Blood glucose levels above the target
Type 1 diabetes/ type 2 diabetes	> 70% (16 h 48 min)	70–180 mg/dl	< 4% (< 1 h) < 1% (< 15 min)	< 70 mg/dl < 54 mg/dl	< 25% (< 6 h) < 5% (< 1 h 12 min)	> 180 mg/dl > 250 mg/dl
Elderly individuals/ individuals at high risk of hypoglycaemia	> 50% (> 12 h)	70–180 mg/dl	< 1% (< 15 min)	< 70 mg/dl	< 10% (< 2 h 24 min)	> 250 mg/dl
Pregnant women with type 1 diabetes	> 70% (16 h 48 min)	63–140 mg/dl	< 4% (< 1 h) < 1% (< 15 min)	< 63 mg/dl < 54 mg/dl	< 25% (< 6 h)	> 140 mg/dl

port generated on the basis of the CGM records is the TIR, i.e. the mean time per day spent with the blood glucose levels within the range of target values. Time in range is expressed in hours or as the mean percentage of readings within the range of target glucose levels (corresponding to the mean percentage of time spent during the day with blood glucose levels within the range of target values). The report also includes the time below range (TBR), which indicates the overall duration of hypoglycaemic episodes and the time above range (TAR), as well as the coefficient of variation of (CV) for blood glucose. These are highly valuable parameters for blood glucose control, because they provide information on both glucose levels and their changes (fluctuations) over the entire period analysed.

The 2020 clinical guidelines of Diabetes Poland, concerning the target ranges for glucose levels and time ranges for TIR, TBR and TAR, consistent with the International Consensus on Time in Range, are presented in Table 3. Moreover, in accordance with the International Consensus on Time in Range, the CV for glucose levels should not exceed 36%. In addition to TIR, TBR, TAR and CV, a standard CGM report also includes mean glucose level, the glucose management indicator (GMI) calculated based on the mean glucose level, and the ambulatory glucose profile (AGP) graph, presenting the mean values and range of fluctuations of blood glucose levels at different times of day both graphically and numerically (Figure 1). The development and popularisation of consensus guidelines for the analysis of CGM traces met the expectations of clinicians and patients themselves, because they define the targets that should be aimed at. This enables simple interpretation of the CGM results and provides an opportunity for improving the quality of life and prognosis in patients with type 1 diabetes [8, 9].

Clinical justification for the usefulness of the time in range and related parameters as a complement to glycated haemoglobin assessment

For about three decades, in particular after the publication of the results of DCCT and the United Kingdom Prospective Diabetes Study with



Sensor use (per week)	93% (6 days and 13 hours)
Mean glucose level based on the sensor ±SD	156 ±59 mg/dl
Glucose management indicator (%)	7%
Coefficient of variation (%)	37.7%

Figure 1. Elements of a report on the analysis of continuous glucose monitoring (CGM) records using the report for the Guardian Connect system, Medtronic, as an example. **A** – graph for ambulatory glucose profile, **B** – presentation of the percentage of time for the individual blood glucose ranges: 70–180 mg/dl – target range (time in range), < 70 mg/dl – hypoglycaemia range (time below range, time below range – level 1 hypoglycaemia: 54–69 mg/dl, level 2 hypoglycaemia: < 54 mg/dl), > 180 mg/dl – hyperglycaemia range (time above range, time above range – level 1 hyperglycaemia: 181–250 mg/dl, level 2 hyperglycaemia: > 250 mg/dl), **C** – statistical data

Data from at least 14 consecutive days of the CGM records should be analysed.

participation of patients with type 1 and 2 diabetes, respectively, diabetes control monitoring was based on self-monitoring of blood glucose (SMBG), performed at variable intensities by the patients, and on periodic measurements of HbA_{1c} levels in the blood. Those were the parameters on which diabetes control criteria were based.

In clinical and observational studies conducted in patients with type 1 and 2 diabetes, HbA_{1c} became a marker used for determining the risk of micro- and macrovascular complications of the disease, with lower HbA_{1c} values being indicative of a reduction in this risk. Despite the unquestionable clinical usefulness of HbA_{1c}, the diabetes care community was aware of its flaws. In fact, while reflecting the mean glucose level over a longer period, HbA_{1c} does not provide any information on short-term blood glucose fluctuations, e.g. on the frequency and length of hypoglycaemic episodes and glycaemic spikes. In daily practice, physicians therefore see patients whose HbA_{1c} level is maintained within the individual target range or is close to the treatment target, but who are characterised by high diabetic instability, with numerous hypoglycaemic episodes and significant hyperglycaemic excursions (Figure 2). Regardless of the fact that HbA_{1c} measurements, for example, performed every 3–4 months, are complemented by SMBG carried out several times a day, many of the above-mentioned blood glucose excursions are still not registered by the patient or presented to the physician. Therefore, it was only natural that the search for alternative markers for blood glucose control was continued, as demonstrated by numerous publications on substances such as fructose and 1,5-anhydroglucitol.

A breakthrough occurred in the first decade of the present century, with the approval of rtCGM systems. Owing to the large number of measurements of glucose concentrations in the interstitial fluid over 24 hours, a gradual improvement in the accuracy and precision of such measurements and the development of analytical applications, new diabetes control parameters appeared, which complement the existing model of assessment of diabetes control based on HbA_{1c} and glucose meter readings. The growing group of users of CGM systems, reaching dozens of percent of the whole population of patients with type 1 diabetes in some countries, resulted in the need to develop new diabetes control criteria based on the parameters obtained from CGM. These criteria have now finally been developed by a group of international experts.

The parameter obtained from CGM which is given the most attention in clinical practice is the time spent by the patient with blood glucose levels maintained within the target range, defined as

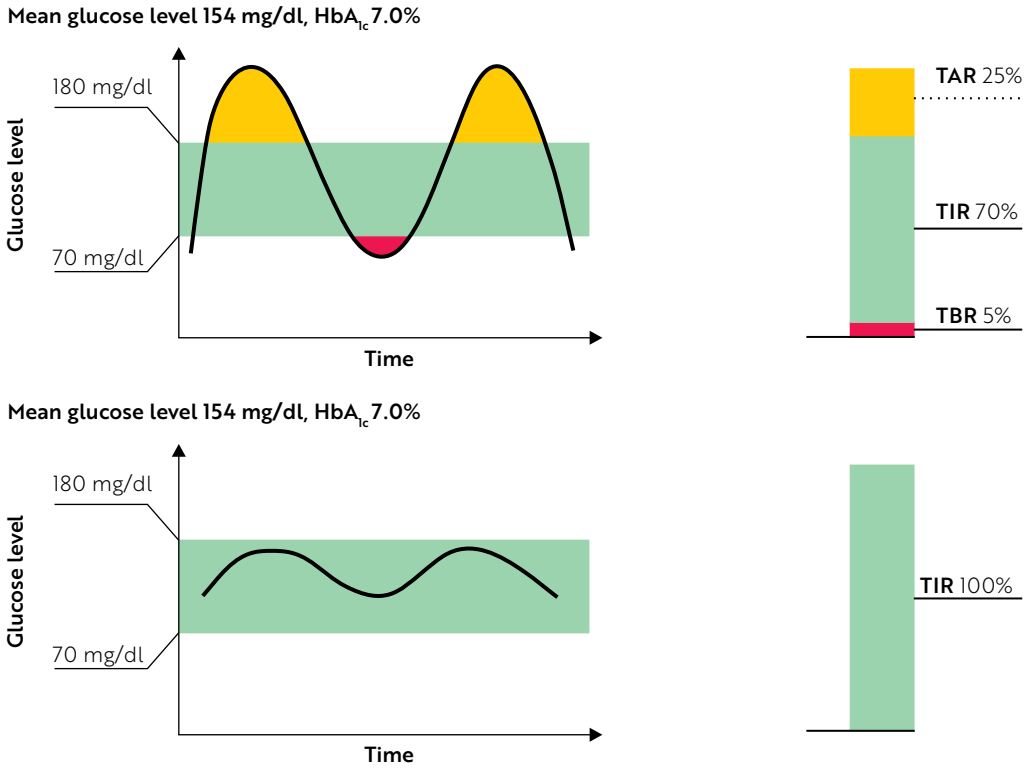


Figure 2. Record of blood glucose levels in three patients with identical glycated haemoglobin levels but different time in range – "different faces" of glycated haemoglobin = 7% (mean glucose level: 154 mg/dl)

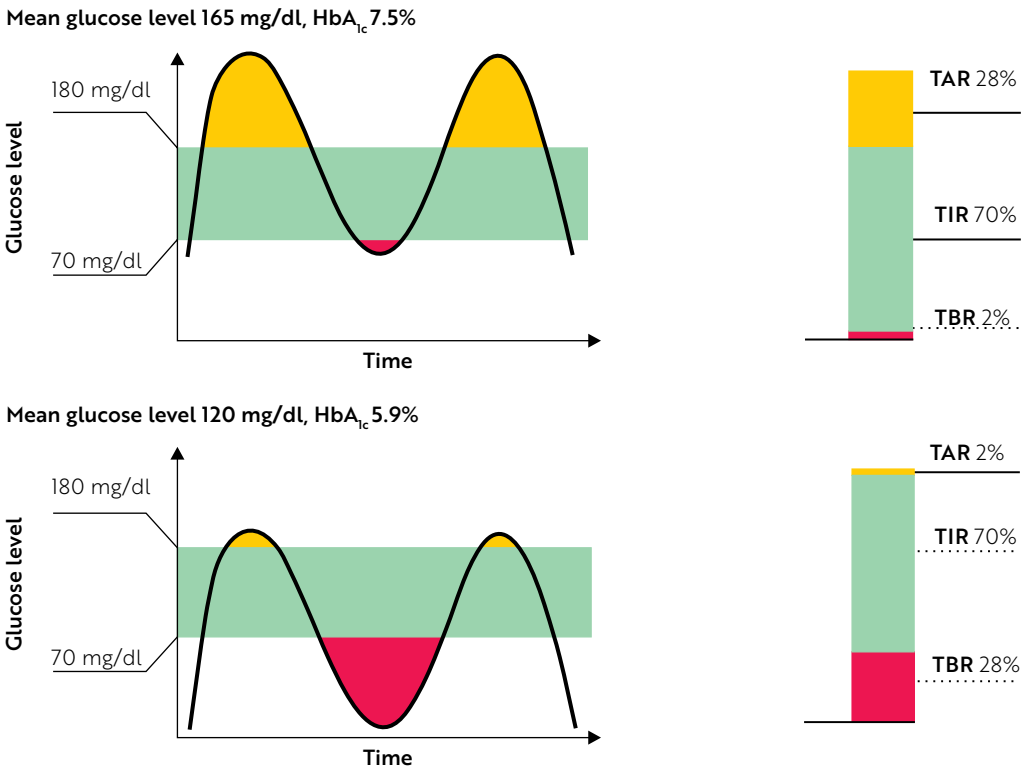


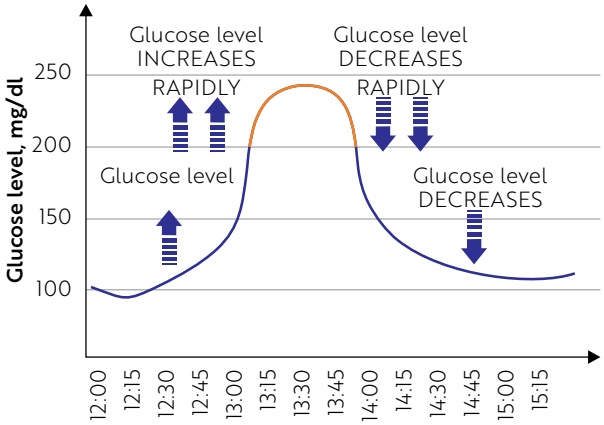
Figure 3. Record of blood glucose levels in two patients with identical time in range levels but different glycated haemoglobin values

glycaemia within the range of 70–180 mg/dl. The exception is women with type 1 diabetes who are pregnant, in whom this range is defined as 70–140 mg/dl. A characteristic of the TIR, lacking in traditional parameters such as HbA_{1c}, is that it not only reflects the averaged glucose level, to which episodes of hypo- and hyperglycaemia also contribute, but also provides an insight into the extent to which the patient succeeds in achieving the desired blood glucose levels with avoidance of such adverse episodes. Time in range value correlates with HbA_{1c} level and, as shown by retrospective analyses, it exhibits a strong relationship with the risk of chronic complications of diabetes. Prospective studies investigating the relationship between TIR and the risk of such complications are expected to take place in the near future. Nevertheless, it should be emphasised that patients with the same TIR value may have significantly different HbA_{1c} values and different interrelations of high and low blood glucose levels (Figure 3). The comprehensive analysis of diabetes control should therefore be complemented by other parameters calculated on the basis of rtCGM records. These are the mean blood glucose level and the time spent with blood glucose below and above the target range (TBR, TAR), and also the parameter which describes the percentage intensity of fluctuations in blood glucose levels, i.e. the CV. When analysed jointly, these parameters reflect the degree of blood glucose control much more comprehensively and accurately than SMBG and HbA_{1c}.

The state-of-the-art blood glucose monitoring systems improve the efficacy and safety of treatment in individuals living with type 1 and 2 diabetes, and patients using CGM systems achieve a durable reduction in their HbA_{1c} value, regardless of the method of insulin administration. Patients who apply CGM systems use far fewer glucose meter strips. The extent of reduction in their use depends mainly on the type of system used for continuous glucose monitoring, as some systems require calibration and glucometric measurement before an insulin bolus is administered. Along with further improvements to CGM systems, patients who use these systems can be expected to stop using glucose meters completely within a relatively short time. In current daily medical practice, new parameters obtained from CGM and HbA_{1c} testing complement each other. However, it must be emphasised that the HbA_{1c} value is estimated automatically in applications supporting CGM systems (and referred to as estimated HbA1c, e HbA_{1c} or GMI). The glucose management indicator value correlates well with the biochemically tested HbA_{1c}

percentage and can be obtained without the need for incurring any additional costs or waiting for the laboratory test result. In the near future, it is therefore possible that laboratory measurements of HbA_{1c} will be completely replaced by the GMI. This will be of particular importance for patients with concomitant diseases which may decrease the accuracy of the laboratory measurement of HbA_{1c}, e.g. in individuals with coexisting haemolytic anaemia and in patients undergoing dialysis. Glycated haemoglobin level is usually understated in such patients – it does not correspond to the mean glucose level and it may be similar to that found in an individual whose TIR is higher.

Using TIR and other CGM-based parameters in clinical practice is a qualitative change in the method of assessing the level of blood glucose control, translating into better treatment effects, improvement to the patients' quality of life, and, taking a longer term perspective, changing the risk of chronic complications of the disease [8, 10–13].



Arrows indicate the rate and direction of changes in glucose levels

Figure 4. Information provided by continuous glucose monitoring systems and presented on the screens of the continuous glucose monitoring receivers

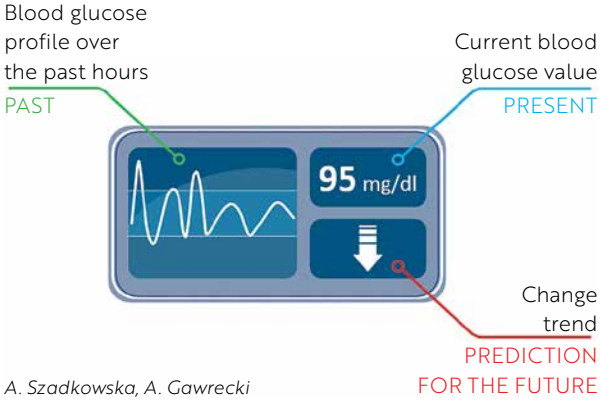


Figure 5. Changes in glucose concentration and an example of the change trend arrows for the receiver of a continuous glucose monitoring system

New dimension of diabetes treatment using real-time continuous glucose monitoring systems – practical aspects of therapy related to the analysis of the current trends in glycaemic changes

The screens on the receivers of all CGM systems display not only the current blood glucose level value and blood glucose profile for the last 3–24 hours, but also the trend arrows. They present the rate and direction of blood glucose changes over the last 15–20 minutes and are predictive for blood glucose changes over the 20–30 minutes following the measurement (Figure 4). Arrows pointing up indicate that the glycaemia value will increase and arrows pointing down indicate that it will drop (Figure 5). The number or positioning of the arrows (vertical, slanted or horizontal) indicates the rate of change.

In the individual CGM systems, the same trend arrows may indicate different rates of blood glucose changes. For this reason, the first thing to teach the user should be what rate and direction of the predicted change in blood glucose is indicated by the individual trend arrows of the given device.

The blood glucose change trend, the "prediction for the future", provides additional and very important information for individuals living with diabetes. For example, when the current blood glucose value is 105 mg/dl (within the normal range) and the trend arrow indicates a blood glucose decrease at a rate of 2–3 mg/dl per minute, this means that the predicted blood glucose value in 20 minutes will probably be approximately 45–65 mg/dl – in this situation, the trend arrow indicates the risk of hypoglycaemia. This information should be taken into account by the patient to appropriately modify the diabetes therapy on the spot based on the blood glucose readout (e.g. when deciding on the insulin dose for a meal or on the steps to be taken before physical activity – "Should I eat an additional portion of carbohydrates or not…?"). Practical rules developed by expert groups are currently available on the interpretation of the trend arrows and on treatment modification, while taking into account the predicted changes in blood glucose. The simplest recommended approach is to increase the insulin dose when a rising trend appears and reduce the insulin dose when a falling trend appears.

On a daily basis, owing to the possibility of predicting the risk of hypoglycaemia, the patient could eat carbohydrates beforehand, thus avoiding its occurrence. What is more, using the information on the rate of blood glucose decrease, the patient could eat the amount of carbohydrates corresponding to this rate, reducing the risk of consequential hyperglycaemia. Consideration of the trend arrows helps people living with diabetes prepare more effectively for activities such as physical exercise, driving a car or sleeping at night.

Since it is the patient who is responsible for ongoing daily blood glucose monitoring and interpretation of trends, the education of CGM users (and in the case of children, their caregivers) should also include basic rules on the immediate modification of therapy based on the trend arrows, in addition to the typical broad spectrum of topics related to daily self-monitoring and prophylaxis against diabetes complications. Such training of diabetic patients may help to prevent hypoglycaemia, increase the TIR and reduce blood glucose fluctuations.

It should be emphasised that in rtCGM systems, in contrast to the intermittently scanned CGM-flash glucose monitoring (isCGM-FGM) systems, the information on the trend in blood glucose changes is not only visible as arrows on the device screen (presented in a continuous manner) but may also be actively reported by the system to the user in the form of glucose rate of change alerts (sounds or vibrations). These alerts may turn the patient's attention to the predicted rapid changes in blood glucose and accelerate the patient's reactions even more effectively, which could constitute a further element contributing towards improved safety and metabolic control in individuals living with diabetes.

When considering the trend arrows after the initial use by the patients of the disease management algorithm proposed by the experts, it may become necessary to correct these arrows. In fact, it is important to bear in mind the patients' individual needs, which arise from their varied lifestyles, diets, types of work, and physical capacity and activity.

As demonstrated by clinical observations, regular consideration of trend arrows in daily diabetes treatment helps patients to improve their blood glucose control. The effectiveness of use of the trend arrows depends not only on patient education, but also on diabetes treatment teams trained in this area motivating the patients to take appropriate action [14–16].

Alarm settings on real-time continuous glucose monitoring systems

Alarms in rtCGM systems complement the function of trend arrows, by providing information on blood glucose values when the patient is not analysing trend arrows, e.g. while sleeping or busy at work. Real-time notifications make it possible to react to changes in blood glucose levels on an ongoing basis. Owing to this, the alarms increase patients' involvement in controlling their own disease and enable an intervention before the occurrence of hypo- or hyperglycaemia, which increases the patient's safety, reduces blood glucose fluctuations and improves diabetes control.

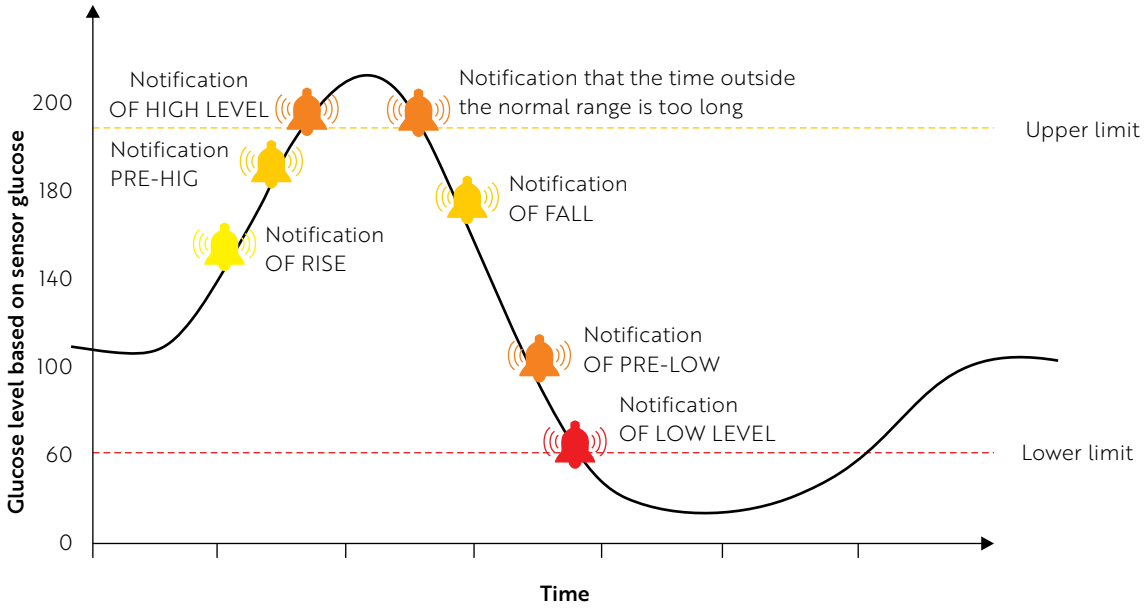


Figure 6. Alarms available in real-time continuous glucose monitoring systems

Table 4. Types of glucose level alarms in real-time continuous glucose monitoring systems and their importance

Upper and lower limits of glucose concentration measured by the rtCGM sensor glucose	Notifications related to high/low sensor glucose (hyperglycaemia/ hypoglycaemia) are configured based on these threshold glucose level (sensor glucose) values
Notification pre-high/low SG	Predictive alarm – a notification generated when the glucose level approaches the upper/lower SG limit; owing to this alarm, the patient is given advance notice of an impending episode of hyperglycaemia/ hypoglycaemia
Notification of high/low SG	Threshold alarm – the system notifies the user when SG reaches or exceeds the upper/lower limit
Notification of SG rise/fall	Trend alarm – the system notifies the user when SG rapidly rises/falls; it shows SG fluctuations after meals
Reminder that the time outside the SG range is too long	Notifies that the duration of hyperglycaemia/hypoglycaemia is too long

rtCGM – real-time continuous glucose monitoring, SG – sensor glucose; glucose concentration measured by the rtCGM sensor

The currently available rtCGM systems offer different kinds of notifications in the form of sounds and/or vibration (Figure 6, Table 4):

- hypoglycaemia threshold alarm (low glucose notification) and hyperglycaemia threshold alarm (high glucose notification);
- trend alarm, i.e. an alarm signalling a rapid rate of change in glucose levels – warning that the glucose level is decreasing rapidly (glucose fall notification) or increasing rapidly (glucose rise notification);
- early warning alarm before the glucose level starts to change rapidly, i.e. the predictive alarm, warning when blood glucose is approaching the threshold (limit) of hypoglycaemia (pre-low notification) or hyperglycaemia (pre-high notification);
- alarm reminding that the time outside the normal blood glucose range is too long.

The alarm settings are adjusted to the needs of each individual patient, for example, taking into account diabetes control, fear of hypoglycaemia, hypoglycaemia unawareness, insulin sensitivity, types of devices used, physical activity, time of day, and experience with rtCGM use. Real-time continuous glucose monitoring systems allow individual setting of various threshold values for hypo- and hyperglycaemia alarms during daily activity and when sleeping. The alarm settings will need to be modified over the course of rtCGM use.

In patients with type 1 diabetes, the use of rtCGM with the hypoglycaemia alarm turned on at a glucose level of 80 mg/dl has been shown to reduce the frequency of hypoglycaemia ≤ 65 mg/dl by over 40% in comparison to the use of rtCGM with the alarms switched off.

The predictive alarm gives the patient the opportunity to react quickly to ongoing changes in blood glucose, allowing severe hypoglycaemia and acute hyperglycaemia to be avoided. It provides an opportunity to intervene before hypoglycaemia or hyperglycaemia manifests. Research studies indicate that predictive alarms substantially decrease the incidence of hypoglycaemia when compared with the CGM system without this function, regardless of the level of glucose concentration that has been set as the alarm threshold. Furthermore, the use of the predictive alarm for hypoglycaemia reduced the incidence of hyperglycaemia > 250 mg/dl, which may be associated with a reduction in excessive consumption of carbohydrates during an episode of hypoglycaemia [17–19].

Clinical usefulness of alarms in real-time continuous glucose monitoring systems

In the treatment of diabetes, it is extremely important for the patient to know what his or her current glucose level is and the direction in which it is changing. Alarms in rtCGM systems make the patients feel that their safety is monitored for 24 hours a day and they will receive timely information allowing them to avoid a potentially dangerous situation. In some cases, real-time CGM systems may play the role of a "guardian angel" – monitoring glycaemic patterns and trends and intervening to warn the patient about potentially dangerous events related to glucose levels, so as to enable the patient to take the appropriate actions in advance.

Real-time continuous glucose monitoring devices fitted with alarms enable the patients to react immediately to prevent impending hypo- or hyperglycaemia. They also provide an insight into how factors such as the type and size of a meal, the type and intensity of physical activity and concomitant diseases affect glucose levels. Real-time continuous glucose monitoring devices allow gly-

caemic variability to be assessed and facilitate recognition of glycaemic patterns, helping the patient and members of the diabetes care team to optimise treatment and improve metabolic control of the disease. Continuous glucose monitoring systems with programmable alarms, which warn the user about current or impending low or high glucose levels, offer additional benefits related primarily to improved patient safety.

The use of these devices by both patients using personal insulin pumps and those using pens for insulin delivery improves HbA_{1c} levels by 0.3–0.6%, without increasing the incidence of hypoglycaemia, and reduces the duration of hypoglycaemia by over 70% in individuals with type 1 diabetes and coexisting hypoglycaemia unawareness.

Continuous glucose monitoring alarms are particularly important for patients at high risk of hypoglycaemia. Real-time continuous glucose monitoring systems fitted with alarms have been shown to more effectively shorten the time spent in hypoglycaemia in individuals with type 1 diabetes and hypoglycaemia unawareness than the intermittently scanned continuous glucose monitoring-flash glucose monitoring (isCGM-FGM) system, which does not have an alarm function. Moreover, rtCGM users had a lower level of fear of hypoglycaemia, which is one of the main barriers to optimum control of diabetes. The change of therapy from isCGM-FGM to rtCGM significantly reduces the incidence of hypoglycaemia in the high-risk population. These observations are consistent with the British guidelines issued by NICE (National Institute for Health and Clinical Excellence), based on which rtCGM systems fitted with alarms and alerts should be the blood glucose control method of choice for individuals with type 1 diabetes who are at high risk of hypoglycaemia.

Real-time continuous glucose monitoring systems have many options for customising alarm settings and adapting them to the needs of the specific user. Some systems are fitted with three different types of protection from dangerous glucose levels – they allow the setting of threshold, rate of change and predictive alarms/alerts.

Diabetic patients who use rtCGM must be well trained in how to insert the sensor under their skin, calibrate the system and interpret the data in real time. They must understand the significance of trends and predictive alarms to appropriately react to the rtCGM data they observe.

Guardian Connect (one of the rtCGM systems) is the first and only independent rtCGM device that can warn its users about potentially low and high glucose levels as early on as 60 minutes in advance. The results of the completed studies clearly demonstrate that predictive alarms considerably reduce glycaemic variability which would manifest without their use. The rate of change alerts may be useful for the detection of patterns of glycaemic changes (e.g. within 24 hours) and for adjusting the insulin therapy to these patterns in a specific patient.

The process of periodic transmission of data collected by the CGM system to a computer program is important, not only for the customisation of alarm settings, but also for the optimisation of basal insulin doses, carbohydrate exchange (i.e. indirectly prandial insulin doses) and the insulin sensitivity index. For example, access to the CGM reports enables the treatment team to assess the timing of bolus administrations before meals and to determine the effect of physical exercise and other daily events on blood glucose levels. Many patients are able to achieve very good blood glucose control as a result of reasonable adjustments of their treatment to their daily lifestyles, which is possible, inter alia, owing to the use of CGM reports and appropriately set alarms. Numerous studies conducted so far have demonstrated that the availability of real-time alarms may help patients to shorten the time spent in the hypo- and hyperglycaemic range and lower the HbA_{1c} value, without increasing the risk of hypoglycaemia.

Devices which not only inform the patient that the hypoglycaemia threshold has been reached or that there is a risk of its development but also autonomously stop the pump without the involvement of the user have been available on the market for a few years. This happens when hypoglycaemia has already occurred (MiniMed Veo pump) or before it occurs, i.e. in a situation where there is a risk of hypoglycaemia (MiniMed 640G pump with the SmartGuard technology, that suspends insulin delivery before the "glucose low"). The principles of operation of these devices are discussed in the next section. What is important is that the clinical evidence for the efficacy of such systems is very strong.

In one of the studies, patients using the MiniMed Veo pump were found to have an almost 40% reduction of the area under the curve (AUC) for blood glucose levels below 70 mg/dl. The time in the hypoglycaemic range of 51–70 mg/dl was shortened by approximately 25%, and the time in the hypoglycaemic range below 50 mg/dl was

shortened by over 50% in comparison with therapy with a standard insulin pump not coupled with rtCGM. At the same time, no significant changes in HbA_{1c} values or more frequent hyperglycaemic episodes were observed.

On the other hand, it has been demonstrated for the MiniMed 640G pump with the SmartGuard function, i.e. with an option of "stopping before low glucose", that the system effectively reduces hypoglycaemic episodes in patients with type 1 diabetes in all age groups, without increasing the risk of adverse events. In a study conducted in adults with type 1 diabetes with a tendency to hypoglycaemia, the use of MiniMed 640G substantially reduced the incidence of hypoglycaemia in comparison with treatment with an insulin pump without the CGM function. Importantly, this effect was achieved without increasing the HbA_{1c} percentage. The improvement in clinical outcomes was more evident during the night, when hypoglycaemic episodes are particularly problematic. Furthermore, patients using the SmartGuard function were less afraid of hypoglycaemia and their treatment satisfaction was higher [19–28].

Continuous glucose monitoring systems integrated into a personal insulin pump: a new dimension in safety and optimisation of metabolic control in the patient

The continuous glucose monitoring systems integrated into a personal insulin pump that are currently available on the market belong to four generations of these devices:

first generation: the personal insulin pump is integrated in a single device with the CGM system, but the system does not take any autonomous actions based on the CGM recording without user involvement (MiniMed Paradigm real-time (722) pump);

second generation: the system suspends insulin delivery from the insulin pump (for 2 hours) based on the CGM recording when the patient reaches the predefined low blood glucose limit (MiniMed Veo pump);

third generation: based on the CGM recording, the system suspends insulin delivery from the pump suitably in advance (predictively), preventing hypoglycaemia and stabilising glucose concentrations (MiniMed 640G pump);

fourth generation: the advanced hybrid insulin pump (MiniMed 780G, an example of the partially "closed loop" system), which not only automatically prevents hypoglycaemia similarly to the 640G pump, but also autonomously corrects hyperglycaemic episodes, making it possible to obtain excellent treatment outcomes with only minimal involvement of the patient.

Because first- and second-generation devices will gradually be withdrawn from the market, systems that belong to the third and fourth generations – MiniMed 640G and MiniMed 780G – are described below.

The newest trends in the development of state-of- the-art technologies used in the treatment of diabetes requiring insulin therapy can be summarised as follows:

- efforts to increase treatment safety through minimisation of the risk of hypoglycaemic episodes;
- autonomous performance of certain therapeutic interventions through the integrated CGM-pump system without the need for their confirmation by the user, which improves the patient's comfort in everyday life and also limits the time actively spent by the patient every day on making decisions related to his or her diabetes treatment;
- development of technologies that simplify diabetes treatment and "forgive" minor errors made by the patient in relation to the treatment.

The MiniMed 640G personal insulin pump has all the characteristics listed above. It is equipped with a real-time rtCGM system with all its benefits, but the most important element that makes MiniMed 640G really unique is the SmartGuard function [29, 30]. Owing to the SmartGuard technology that uses rtCGM, the device autonomously suspends insulin delivery, without the need for confirmation by the patient, in situations where the glucose level in the patient is approaching values that correspond to hypoglycaemia but where these values have not yet been reached. The device resumes insulin administration once the glucose level has stabilised.

There are many advantages to this solution. The most important include:

- the possibility of almost complete protection of the patient from severe hypoglycaemia (i.e. from a substantial lowering of glucose concentrations to the point where the patient requires the help of another person). In contrast to second-generation CGM-pump devices, insulin delivery is suspended sufficiently in advance in MiniMed 640G so as to effectively prevent hy-

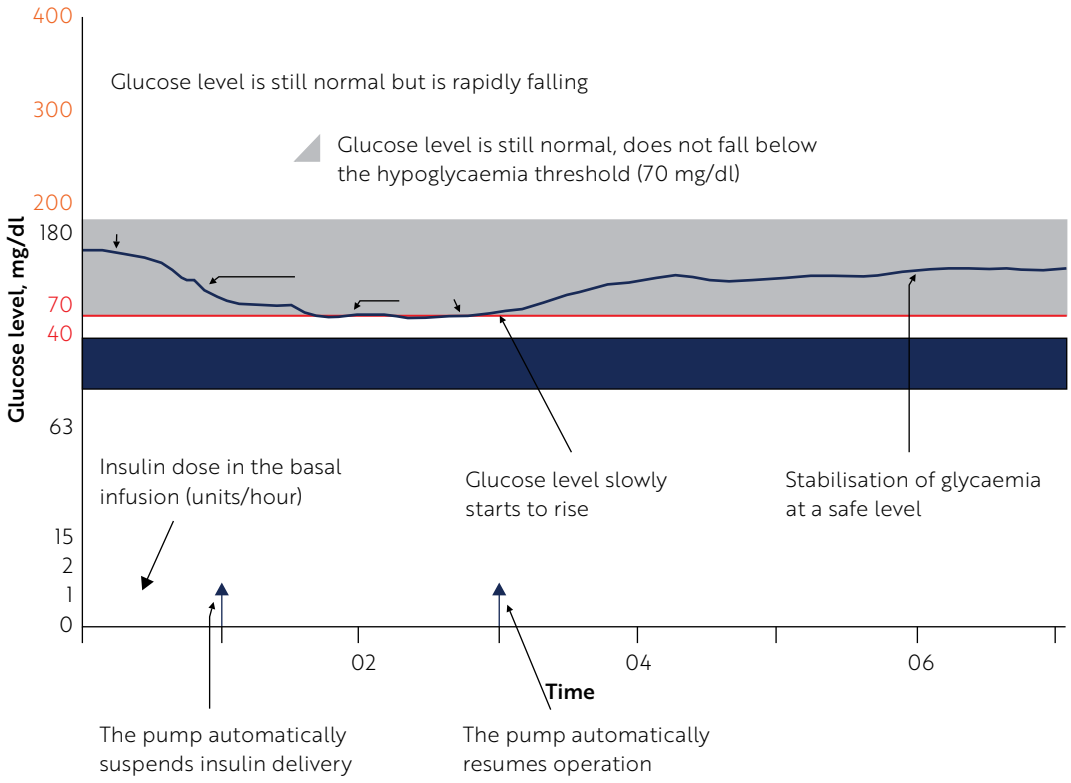


Figure 7. Practical operation of the SmartGuard technology using real-time continuous glucose monitoring (MiniMed 640G) during the night. All actions presented in the figure are taken automatically by the system and do not have to be approved by the patient. Without taking any action, the patient is protected from hypoglycaemia and glycaemia stabilises at a safe level

poglycaemia (Figure 7), and not only once it has already occurred. The device also helps to eliminate most episodes of minor hypoglycaemia and only sometimes to avoid it. Patients using this technology should eat an additional small portion of carbohydrates;

- higher sense of user security, especially at night;
- significant improvement in comfort in the patient's life (and that of his or her family), for example, related to:
  - » the possibility of switching off a number of alarms that warn of hypoglycaemia, which is particularly important during the night, because the patient is not woken up when there is a risk of hypoglycaemia and the device automatically protects the patient from low blood glucose levels,
  - » the possibility of slightly less precise calculations of carbohydrate content in meals: the insulin dose per meal can be administered with a slight "overage", because if there is a risk of hypoglycaemia, the device will automatically suspend insulin delivery,
  - » no need for modifying the basal infusion of insulin after physical exercise;
- more effective body weight control (the patient has to eat simple carbohydrates less frequently in relation to the treatment of hypoglycaemic episodes);
- owing to effective protection from hypoglycaemia, the device enables a slightly more "aggressive" (in a positive sense) insulin dosage, increasing the percentage of TIR and protecting the patient from the development of chronic complications of the disease.

The personal insulin pump with SmartGuard technology is a technological breakthrough that enables a significant improvement in metabolic parameters and a very substantial improvement in quality of life for people living with diabetes. It should be emphasised that, without this device, many patients with type 1 diabetes would not be able to pursue their professional lives, procreational, sport-related and other plans [29, 30].

MiniMed 780G is an even more technologically advanced device supplied by Medtronic that has been approved in Europe [31, 32]. This pump, called an advanced hybrid pump, represents a new frontier in the quality of treatment of type 1 diabetes. The device not only has all advantages of the 640G pump, but also corrects hyperglycaemia through the automatic administration of additional insulin doses. The device measures the glucose level every 5 minutes – if it notes a rising trend,

it may increase the rate of basal insulin infusion or administer an additional insulin dose, called an autobolus. It should be emphasised that these additional insulin doses are administered not only based on the current blood glucose level, but also considering a number of other treatment parameters, including, for example, the trend and rate of change in blood glucose. They are therefore often referred to as "smart insulin boluses", which, on one hand, very effectively correct hyperglycaemia and, on the other hand, prevent unnecessary overdoses of insulin. Clinical trials have demonstrated unprecedented efficacy for this technology in the optimisation of metabolic control measured, for example, as the percentage of TIR [31, 32]. However, substantial benefits related to quality of life of the patient should also be noted: a number of previous duties of the patient, which were very cumbersome and time-consuming, are taken over by the device, and signalling the intake of meals remains one of few remaining obligations of the patient. This device can definitely be called "the technological artificial pancreas".

Importance of technologies based on real-time continuous glucose monitoring for the patient's quality of life and possibility of taking up professional and physical activity

Advances in the treatment of type 1 diabetes have prolonged patients' lives and limited the occurrence of acute and chronic complications of this disease. This made it possible to improve quality of life for the patients, closely correlated not only with their state of health, but also professional and social activities and taking up physical exercise. The American Diabetes Association recommends screening tests for depression as a standard in routine care of patients with type 1 diabetes, because they are at higher risk of depression than the general population and the relative risk of suicide is estimated as 2.25. An improvement in quality of life was found in numerous studies conducted on treatment using insulin pumps or CGM systems, as well as devices combining both these technologies. In these studies, the following scales were used to assess self-perception of health and quality of life in patients with diabetes and a high burden of disease: health-related quality of life, Diabetes-Specific Quality of Life Scale, Diabetes Treatment Satisfaction Questionnaire, short form health survey, problem areas in diabetes. An improvement in quality of life was found after the use of CGM in some of these studies, regardless of the insulin therapy model.

The purposes of the diabetes care system include development and strengthening of the sense of responsibility for their own health in people living with diabetes, as well as strengthening of their position as employees and counteracting their exclusion from the labour market. There have been single studies indicating a deterioration of metabolic control of type 1 diabetes in patients working in shifts. Occupational physicians make medical certification decisions on the basis of the written opinion of a diabetologist. Self-evidently, CGM increases an employee's safety, especially at night, while operating machinery and driving.

Frequent occurrences of moderate hypoglycaemia, severe hypoglycaemic episodes or hypoglycaemia unawareness are contraindications for practising many professions. It is possible to eliminate these contraindications on condition that the patient uses CGM and is able to correctly interpret blood glucose results and to correctly respond to blood glucose alarms. In particular, this applies to the principles of medical certification for drivers with diabetes, formulated by Diabetes Poland in its clinical guidelines.

Continuous glucose monitoring systems that can be connected to the Internet cloud enabled the development of telemedicine. Consultations conducted using information and communication technology systems save patients' time, as they do not have to travel long distances to discuss the current blood glucose results with a diabetes specialist and obtain treatment modification advice from the specialist. Owing to this, the professional activity of people living with type 1 diabetes is less limited.

Numerous benefits of the use of CGM, in particular rtCGM, that are emphasised in this paper have a direct and multifaceted effect on the reduction of employee absenteeism. Both the employee and employer are affected by the legal and financial consequences of absence at work. Informed and unlimited use of CGM systems by patients may reduce the phenomenon of occupational discrimination of persons with type 1 diabetes and increase their productivity at work.

The occurrence and fear of hypoglycaemia still remain the greatest barriers that limit the taking up of physical activity by people living with type 1 diabetes. It is particularly difficult to maintain normal and stable blood glucose levels during moderate to maximum intensity exercise. This type of physical

exercise may cause delayed hypoglycaemia, including nocturnal hypoglycaemia. Currently, the most effective method of prevention of such hypoglycaemic episodes is the use of continuous glucose monitoring systems integrated into insulin pumps, that enable automatic suspension of insulin delivery. The predictive low glucose suspend function, for example the SmartGuard algorithm in the MiniMed 640G system, with the appropriately programmed low glucose threshold, also makes it possible to limit hypoglycaemic episodes during physical exercise. The Diabetes Poland clinical guidelines define the principles of determining the eligibility of people living with type 1 diabetes for practising sports, with consideration of professional and extreme sports. In line with the Diabetes Poland position, the use of CGM systems is recommended while practising high-risk sport disciplines [33–44].

Telemonitoring as an innovative tool in diabetes care

At present, many glucose meters and all CGM systems have a feature of continuous data transfer to the Internet (IT) cloud using the IT devices designated for this purpose, which enables telemonitoring. This is also true for insulin pumps. Data transfer may be synchronous (in real time) or asynchronous (when patients periodically read/send the data). The recipients of this information are both diabetes treatment teams and families of diabetic patients.

The use of state-of-the-art technologies for blood glucose monitoring and insulin therapy, combined with information and communication technology tools, makes it possible to introduce clinically effective tele- medicine into the diabetes care sector. The effectiveness of remote medical consultations depends on many factors. The quality of data management systems, i.e. of the software for the reading and analysis of blood glucose data obtained from the devices used by patients, is of major importance. Currently, the vast majority of the computer programs designated for CGM systems enable quick analysis of the acquired data according to international guidelines. Since the software and databases used for this purpose are located in Internet clouds, diabetes care centres must have computers with continuous Internet access. Furthermore, both the treatment team members and patients must undergo training in the use of the respective IT tools.

Telemonitoring use of CGM by patients enables the physicians to more comprehensively analyse blood glucose control parameters than is the case when using glucose meters alone. The information on the TIR and on the remaining parameters for the AGP makes it possible to better assess metabolic control of diabetes and formulate the appropriate recommendations for patients, allowing the remote medical consultation to become more adjusted to the patient's needs.

An increasing number of modern CGM systems are also fitted with applications that enable ongoing transfer of data on the current blood glucose values to members of the family of diabetic patients through the Internet cloud (Table 2). Owing to such solutions, telemonitoring by family members, in particular using rtCGM, improves blood glucose control, as well as the safety and quality of life of the patients.

Telemedicine in diabetology also plays a very important role in the remote education of patients and people around them. Remote training, conducted in synchronous mode or shared via the web for watching at any time, may apply both to the principles of treatment and to the technical operation of the devices that are being used, as well as to the method of analysing blood glucose control parameters and their use in daily life.

The use of telemedicine in diabetes care has been extensively discussed for several years, for example, leading to the publication of the international recommendations for digital/virtual diabetes clinics in August 2020. The clinical guidelines of Diabetes Poland also state that telemedicine has become "an important element of diabetes control optimisation".

The COVID-19 pandemic has accelerated the development of telemedicine worldwide, and diabetes care found its place in the virtual world perfectly. The existing experience has proven that remote medical consultations in diabetes care can essentially replace traditional consultations at outpatient clinics, especially for patients who use CGM systems. The hybrid therapy model using both types of consultations (remote consultations + personal consultations) is slowly becoming everyday reality in diabetes care, and there is much to suggest that it will remain in existence after the end of the current pandemic. It will definitely have to be improved (e.g. through the introduction of video consultations). Several months of experience following the abrupt introduction of telemedicine into diabetes care indicates that the diabetes treatment team should have an additional member – an IT specialist. In Poland, le-

gal approval of remote medical consultations in March 2020 significantly contributed towards the development of telemedicine in diabetology.

Among the recommendations for the care of individuals living with type 1 diabetes during the COVID-19 pandemic, it is very important is to provide them with access to regular and remote consultations, continuous improvement of e-visits and e-education, and increasingly widespread use of CGM and telemonitoring [9, 45, 46].

Optimisation of care of a patient with type 1 diabetes in Poland in relation to disease management methodology and a value-oriented healthcare system

Diabetes is a chronic disease that requires optimum management, as well as comprehensive and coordinated care that is oriented towards maximisation of the health benefits and ensuring cost effectiveness. In this case, disease management involves the provision of active care by the medical service provider for a patient with a chronic disease. The purpose of the implementation of such a management strategy is to focus the activities of a team of healthcare professionals on the actual health requirements of the patients and to satisfy such needs in a comprehensive, planned, continuous and integrated manner. During the implementation of the medical care plan, the patient is an active partner in the decision-making process and obtains the support of a team of healthcare professionals that uses state-of-the-art drug and non-drug medical technologies (including e-health). The healthcare system in Poland should be value-oriented, i.e. it should be a value-based healthcare model. Increased healthcare spending must lead to improved efficacy and effectiveness of care, and also to improved experiences of the patients using the care.

Diabetes and its complications not only generate high direct costs, but also (or even predominantly) very high indirect costs, resulting from the loss of productivity. The cost of diabetes treatment in 2018 was PLN 2.5 billion. Out of this, PLN 2 billion was paid by the National Health Fund (49% – medicines used in the treatment of diabetes, 25% – strips for blood glucose measurements, 22% – medical services provided in relation to diabetes, 4% – insulin pumps and CGM systems) and PLN 0.5 billion was paid by patients. According to the most recent maps of healthcare requirements developed in 2020 by the Ministry of Health, diabetes was responsible for 491,000 disability-adjusted life-years and 342,000 years lived with disability in Poland in 2019. An almost two-fold increase in these categories was noted in comparison with 1990 (Table 5).

Table 5. Disability-adjusted life years and years lived with disability as a consequence of diabetes in 1990, 2009 and 2019

Diabetes mellitus	1990	2009	2019
Disability-adjusted life years	292,000	381,000	491,000
Years lived with disability	190,000	253,000	342,000

The basis for diabetes management and the optimisation of value-oriented care for a patient with diabetes should be clinical standards developed in accordance with the most recent medical knowledge. In Poland, such standards are available as the guidelines of Diabetes Poland that are developed each year. The treatment objectives in diabetes are defined based on the use of drug and non-drug technologies for blood glucose monitoring and insulin delivery. A breakthrough that contributed towards an improvement of care for diabetic patients in Poland was this disease (together with cardiovascular disorders and also cancer and respiratory system disorders) being entered into the list of national health priorities defined by the Regulation of the Minister of Health of 27 February 2018. Evidence for the implementation of this priority was provided by the reimbursement decisions made in 2018–2020, which led to a significant improvement in diabetes patient access to publicly reimbursed new drug and non-drug technologies (Table 6).

The measurements of effectiveness of care should include the whole diagnosis and treatment pathway of a diabetic patient. The Strategy of the National Health Fund developed in 2019 for the years 2019–2023 recommends "continuous measurement of the efficacy of measures". Insulin pumps with an integrated or separate CGM system make it possible to not only adequately administer insulin, but also to concomitantly provide the physician, nurse and patient with the data required for effective treatment monitoring, sent electronically or placed in the cloud. Diabetes Poland has requested and recommended reimbursement of the modern CGM systems for a broader group of patients on multiple occasions. The current advances in the diagnosis and monitoring of diabetes treatment enable optimisation of care and a significant reduction of complica-

Table 6. Reimbursement decisions taken by the Minister of Health with regard to new drug and non-drug technologies in diabetes in 2018–2020

The following drug technologies were covered by reimbursement:	The following non-drug technologies were covered by reimbursement:
Long-acting insulin analogue (degludec), short-acting insulin analogue, combination: insulin aspart + insulin degludec	Real-time continuous glucose monitoring system for children and adolescents with type 1 diabetes up to 26 years of age (meeting the specified conditions (Tables 1, 2, 3)
Flozins (SGLT-2 inhibitors): empagliflozin, dapagliflozin, canagliflozin	Flash glucose monitoring-sensor for children and adolescents with type 1 diabetes aged 4 to 18 years.
Incretins (GLP-1 analogues): dulaglutide, semaglutide	Dressings for cleaning wounds for diabetic foot therapy
Free-of-charge medicines for pregnant women	

Table 7. Current reimbursement status of medical devices in diabetes

Under separately contracted services (SOK):	Under reimbursement of medical devices:
Treatment of diabetes using an insulin pump in children Treatment of diabetes using an insulin pump in adults	1. Infusion sets for a personal insulin pump (including the cannula, connector and tubing) for: • individuals up to 26 years of age, 0% co-payment by the medical service recipient, • individuals above 26 years of age, 30% co-payment by the medical service recipient, • pregnant women, 0% co-payment by the medical service recipient. 2. Reservoir for insulin for a personal insulin pump, 30% co-payment by the medical service recipient. 3. Sensor/electrode for a rtCGM system, 30% co-payment by the medical service recipient up to 26 years of age – patients up to 26 years of age with type 1 diabetes treated using an insulin pump, with hypoglycaemia unawareness (no prodromal symptoms of hypoglycaemia, with exclusion of post-alcohol hypoglycaemia). 4. Transmitter for an rtCGM system, 30% co-payment by the medical service recipient up to 26 years of age – conditions as in section 3. 5. Flash glucose monitoring sensors for patients between 4 and 18 years of age with type 1 diabetes, with excellent monitoring of glycaemia, i.e. with at least 8 blood glucose measurements per day (they cannot be ordered for a patient using rtCGM), 30% co-payment by the medical service recipient recipient.

rtCGM – real-time continuous glucose monitoring, SOK –

tions. Approximately 30% of diabetic patients do not achieve the target blood glucose values, which is definitely an important problem in modern diabetology, because it translates into acute and delayed complications of diabetes and premature deaths. Phone consultations, remote blood glucose monitoring, for example using rtCGM systems, and video consultations are the most commonly investigated telemedical interventions. Each of these leads to increased access to specialist diabetes care. Many new technological solutions (which include CGM systems) are already partially reimbursed for children and adults up to 26 years of age with type 1 diabetes, but they are still not available for older patients, regardless of the fact that, in line with clinical trials, the use of such solutions translates into an improvement of glycaemic control and into a reduction in the risk of hypoglycaemia. The National Health Fund currently reimburses the medical services listed in Table 7 for diabetes treatment.

The age limitation for the use of insulin pumps and CGM systems is an example of a paradox of the Polish healthcare system, where there is no continuity of optimum healthcare when the patient moves into the next age group. In collaboration with representatives of patient communities, the Bureau of the Commissioner for Patients' Rights developed a model solution for the problem of individuals with the onset of a chronic disease in childhood, who have been treated within the paediatric care system, and for their transition to the healthcare system for adults. The model, called Good Practices, is based on three assumptions: placing the patient within the healthcare system, knowledge of the particularities of the

diseases and developmental changes during adolescence, and proper education of the patient.

The use of personal insulin pumps and CGM systems in patients with type 1 diabetes is recommended by Diabetes Poland in its 2020 Clinical Guidelines and the report "Significance of modern blood glucose monitoring methods and telemedicine for improvement of quality of care for patients with diabetes". In view of the above issues, the introduction of public reimbursement is also recommended for personal insulin pumps and real-time CGM systems for patients with type 1 diabetes with hypoglycaemia unawareness above 26 years of age [47–56].

Conclusions

Continuous glucose monitoring was initially only treated as a tool for research studies. It was believed that its use in clinical medicine would be unnecessary and that such devices would only play the role of an expensive gadget. However, over the past two decades, extensive scientific evidence has been obtained on the immense benefits of CGM – we currently know that this method leads to a significant improvement of metabolic control in diabetes. In fact, owing to access to continuous information on blood glucose values, the patient makes optimal decisions as to the insulin dose, nutrition, etc. Over the past 3 years, it has been demonstrated that patient use of CGM is more important for effective diabetes control than the use of any specific method of insulin administration. It is therefore possible to state that CGM has also become a sort of a medicine – its implementation improves diabetes treatment outcomes.

As a result of the more widespread use of CGM and the rapidly increasing pool of scientific data, the information obtained from this system allowed the setting of new standards for glycaemic assessment, in other words, provided new tools for assessment of the correctness of metabolic control of diabetes (or the lack of such control). In clinical practice, we have recently started to use the term TIR, i.e. the parameter defining the quantity of time within 24 hours during which blood glucose was within the optimum range for the given patient; it is also possible to assess the length of time during which blood glucose was too low or too high. This method of assessing metabolic control of the disease is far more valuable and helpful for the patient than random measurements of the HbA_{1c} percentage performed every few months, or even measurements of blood glucose levels using a glucose meter several times per day.

The term TIR, only applicable when CGM is used, almost perfectly reflects the efficacy and safety of insulin therapy. This parameter has become the subject of standards developed by international expert groups that define its desirable ranges, and is also a constant element in clinical guidelines on the management of patients with diabetes, including those developed by Diabetes Poland. It is now up to the physicians and individuals responsible for the healthcare system to create the conditions that will enable the CGM systems to be used by each patient with type 1 diabetes whose involvement with the treatment and level of knowledge about diabetes treatment allow for their proper use.

Summing up, the currently available CGM systems, in particular rtCGM, make it possible to:

- administer insulin in a manner that is closest to its physiological secretion (i.e. effective and safe);
- safely maintain blood glucose levels within the normal or almost normal range;
- optimise patient behaviour as regards the diet and professional and recreational activities;
- almost completely avoid significant hypoglycaemia;
- prevent acute hyperglycaemic complications of diabetes (acidosis/ketoacidotic coma);
- in a longer term perspective, also reduce the incidence of chronic diabetic complications.

As mentioned above, the introduction of glucose meters into clinical practice in the 1980s revolutionised diabetes treatment, dramatically increased patients' participation in its management and had immense educational value – patients started to learn quickly how their behaviour affects the blood glucose value. However, glucose meters were only a prelude to another revolution – complete assessment of blood glucose, which is currently possible owing to the use of continuous monitoring systems. Within a very short time, CGM has become a standard for people living with type 1 diabetes using pump therapy, but identical benefits are also obtained from CGM by patients treated using the traditional method of multiple insulin injections. Unquestionably, enabling more extensive use of CGM by people living with type 1 diabetes in Poland will be a major step forward in improvement of the quality of diabetes treatment, quality of life for patients and prevention of acute and chronic complications of this disease.

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Conflict of interest

The authors declare no conflict of interest.

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