Application of high technologies in modern diabetology

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Abstract. Currently there are two types of devices determining blood glucose level on an ambulatory basis: self-monitoring of blood glucose using glucometers (Self-monitoring of blood glucose, SMBG) and various CGM devices (Continuous Glucose Monitoring) - continuous monitoring systems glucose. Nowadays CGM can definitely be called "ECG diabetes" and it is widely used in medical practice to treat the disease. Continuous monitoring of blood sugar level becomes the necessary tool for motivating people to change their lifestyle and it is very important component of effective treatment. With a therapeutic approach from the position of a “gravicentric concept” based on lowering glucose level by reducing the patient’s weight, remission of the disease and complete restoration of carbohydrate metabolism are no longer a myth. According to recent researches the transition of therapeutic goals from blood glucose targets (HBA1C) to metabolic goals (reducing body mass index - BMI) leads to quick results. The interpretation of CGM monitoring data based on a clinical example is described. CGM monitoring shows that in patients with T2DM the coefficient of variability is an easily accessible and most informative index confirming the restoration of functional abilities and secretion of endogenous insulin through metabolic recovery.

Currently, the number of people with type 2 diabetes mellitus (T2DM) is growing steadily. According to the International Diabetes Federation (IDF), today there are about half a billion people in the world who suffer from this disease, one third of which is people over 65 years old (figure 1) [1].

Figure 1. The total number of diabetes patients is growing steadily.
IDF estimates that diabetes mortality rates exceed those associated with other non-communicable diseases.

Insulin deficiency or cells inability to respond to insulin (IR, insulin resistance) leads to high blood glucose levels (hyperglycemia). Without controlling for a long time, hyperglycemia can cause severe complications, such as cardiovascular diseases, neuropathy, nephropathy, eye diseases. A sharp decrease in blood glucose levels (hypoglycemia) can lead to loss of consciousness, convulsions or death. Frequent hypoglycemic states are fraught with brain damage and cognitive impairment. Diabetes also exacerbates major infectious diseases such as tuberculosis, HIV / AIDS and malaria.

Treatment methods in modern diabetology undergo significant changes. Previously, the approach to the treatment of T2DM, where the main therapeutic goal is to reduce body mass index (BMI), was called the "gravicentric concept" [2].

This technique is aimed at the gradual de-intensification of sugar-lowering pharmacotherapy as eliminating excess body mass which is one of the leading pathogenetic mechanisms of the development and progression of the disease.

One of the most important factors contributing to the understanding profound changes that underlie the disease is the introduction of high technology into everyday practice. Currently, there are two types of devices designed to determine the value of glucose in the blood on an outpatient basis: self-monitoring of blood glucose with glucometers (Self-Monitoring of Bloodglucose, SMBG) and various CGM devices (Continuous Glucose Monitoring) which are continuous glucose monitoring systems.

Millions of people with diabetes measure their blood glucose with glucometers which are portable blood glucose monitoring systems. These devices measure glucose in capillary blood, usually taken from the finger. Since the 1990s, monitoring of glucose levels on an outpatient basis has become commonplace. SMBG is also used by medical professionals in various medical institutions. Throughout the 1990s, technological advances made these devices more reliable, compact and easy to use [3].

However, single SMBG measurements do not show the full picture of the change in blood glucose in the patient's body, since this parameter can change almost every second (figure 2).

![Figure 2. Even patients with acceptable A1C levels can experience glycaemic variability that can be determined by CGM only.](image)

Sharp fluctuations in glucose levels, which are of great danger to the patient, may go unnoticed, even if the check is performed every hour.

Unlike SMBG, CGM systems provide a continuous series of glucose readings throughout the day. Moreover, the measurement of glucose concentration is carried out in the interstitial fluid, and not in the
blood. This is due to the fact that the CGM data, as a rule, do not coincide with the SMBG data exactly. In other words, there is the so-called delay effect by equalizing glucose levels in different body environments. However, CGM systems allow you to see how the glucose level changes throughout the day, after eating, taking medicines or physical activity in detail. To evaluate glycaemic parameters correctly, the area of normal glucose values is highlighted in color in the graph displayed on the receiving device (figure 3).

![Figure 3. FreeStyleLibre Receiver (here a smartphone).](image_url)

The patient does not need to puncture his finger constantly as the thinnest capillary sensor is easily implanted in the subcutaneous fat layer, generally for two weeks. The sensor is invisible under clothing, is waterproof and has no discernible effects on living a usual way. A separate unit is used to process information. Modern CGM systems synchronize data with iPhone and Android smartphones. This is especially convenient when the patient is a child as the measurement results can be displayed on his parents’ smartphone.

In addition to the current glucose level and data for the past few hours, CGM devices display real or predicted glycated hemoglobin (HbA1c allows you to predict the average blood glucose level over the next three months), and also show a trend arrow warning a person about changes in his blood glucose level. The trend information reflects the direction of the current glucose trend and the approximate rate of the parameter change; if the arrow is horizontal, glucose level is not changing, if it is pointing up or down, it indicates increasing or decreasing the level of glucose. With this option, the next measurement can be predicted.

Along with trend tracking information, CGMs usually provide users with real-time alerts and alarms. For example, alarms may sound when current glucose values exceed preset thresholds, or there is a dangerous trend for glucose values to change. A person can contact the attending physician, or take the necessary measures independently.

A retrospective analysis of glycaemic parameters that are stored in the memory of the device allows the doctor to get a real picture of the patient’s condition and make adjustments to the treatment promptly.

The first CGM (GlucoWatch G2 Biographer, MedtronicMiniMed) was approved for the US market in 2001 [4]. In subsequent years, other US device manufacturers (Dexcom, AbbottDiabetesCare; Senseonics) also worked well in the EU and the USA. CGM systems are constantly being improved; if the measurement error of the first devices was more than ± 20% [5], then the accuracy of modern systems is much higher (± 10%) [6-9]. The size, weight, complexity and cost of CGM devices have decreased, and the specificity, usability, data management and data analysis software have improved significantly.

Currently, CGM systems available on the market are divided into three categories depending on the design of the device: conventional or personal, professional and “Flash” CGM (FGM) [10].

With personal CGM users can see the graph and the actual glucose value on the display of the receiving device, or with the help of a mobile application on a smartphone or a similar device. The device usually includes options to warn the user about glucose level approaching to hypo- or
hyperglycemic ranges. The main advantage of such devices is that the patient can make immediate changes in his diet, medication, insulin dosage, physical activity. The models that belong to this group of CGM are MedtronicMiniMed® 530G, 640G [11]; Dexcom G4®, G5®, G6® CGM [12].

Unlike personal glucose monitoring, professional monitoring collects data using a “blind” method designed for retrospective viewing by the attending physician. The device records glucose level data, but does not display them through the user interface. Now there are three systems for professional use of CGM: Medtronic iPro2 [13], DexcomProfessional [14] and FreeStyleLibrePro [15]. The main purpose of professional systems is to assess the quality of glycaemic control, the magnitude of the amplitude of glycaemic fluctuations, the time of day with the greatest risk of hypo- and hyperglycemia, to make changes to pharmacotherapy, diet and physical activity.

Today there is one CGM “Flash” system; it is FreeStyleLibre Flash (Abbott) [16], which differs from the above-mentioned CGM classes. The system does not send measurement data to the display device and cannot alert automatically. Instead, the user should bring the display device closer to the sensor, “scan” the data for 1 second in order to see the current glucose reading, data from the last 8 hours and a trend arrow that shows a tendency the blood glucose level to increase or decrease. One of the advantages of FreeStyleLibre is that the system has a factory calibration, so the user doesn’t have to calibrate it.

The design of CGM systems includes the following basic elements: a glucose sensor that is temporarily implanted under the skin, a wireless transmitter (transmitter) that converts the signals of the glucose sensor to glucose concentration, and a receiver that displays the glucose concentration received from the transmitter.

In most sensors the electrochemical (enzymatic) method is used to determine the glucose level; the exception is Eversense CGM, which implements a fluorescence analysis method.

CGM can be installed either by the user on an outpatient basis with the help of a special tool, or it can be implanted subcutaneously by a doctor in a medical institution. After installation, one end of such a sensor is under the skin, and the other end of the sensor is connected to a transmitter, which measures the output signal of the sensor before transmitting data to the display device. In some CGM systems, the transmitter can convert the raw sensor data into calculated glucose values; in other systems, the receiver performs it (figure 4).

The first MedtronicMiniMed sensors were installed for 12 hours, 3 days, then sensors with the period of wearing of 6-7 days (iPro ™ 2, Dexcom G5), 10 days (Dexcom G6), 14 days (FreeStyleLibre) were developed. The Eversense CGM (Senseonics) system is installed for 90 days.

Today, CGM which can be definitely called "ECG diabetes", has become a great part of treating this disease. Continuous monitoring of blood glucose level is a serious tool for motivating patients to change their lifestyle, which is an essential component of effective treatment of the disease. With a therapeutic approach from the position of a “gravicentric concept” based on lowering glucose level by reducing the patient’s weight, remission of the disease and complete restoration of carbohydrate metabolism are no
longer a myth. Recent studies show that this can be achieved quickly as therapeutic goals move from blood glucose targets (HBA1C) to metabolic goals (decrease in body mass index (BMI)).

Here is a typical clinical example. The patient is a woman of 63 years old, who has suffered from T2DM for 13 years. For the past 5 years, she has had pump insulin therapy. During these 5 years, the woman gained a lot of weight (12 kg). She had a myocardial infarction 3 years ago. Attempts at physical education led to severe hypoglycemia, and, as a result, to the complete diet violation; to increase the glucose level, she ate and gained weight again.

Baseline patient data: total daily insulin dose (TDI) is 110 units / day; HBA1C is 6.6%, CV (coefficient of variability) is 28.7%.

Figure 5 shows the results of continuous monitoring of glycaemia before the start of deintensification of therapy.

Judging by the CGM curves, the patient went into prolonged (hours) hypoglycemia (below 40 mg %) during physical activity in the daytime (indicated by an arrow), and at night the threshold of hypoglycemia remained for a long time (the lower glycaemic limit at night was set for her no less than 100 mg %), which could lead to her death.

As a result of the de-intensification of pharmacotherapy for a little more than six weeks, the patient's weight decreased by 10 kg, while she completely stopped taking insulin.

Figure 6 shows the results of continuous monitoring of glycaemia after pharmacotherapy de-intensification. The CGM curves show that the patient has no hypoglycemia, her blood glucose readings are almost normal, CV decreased from 28.7% to 14%.

De-intensification of therapy led to a significant improvement in its metabolic state and to remission of diabetes mellitus, although the patient's HBA1C value did not change.

To confirm metabolic recovery in patients with T2DM, the most informative index is the coefficient of variability. As an example, we take a study in which 18 patients who initially took insulin in combination with metformin and other oral anti-energy drugs. CGM recordings were made before metabolic intervention and immediately after the complete withdrawal of insulin. The average age was 58.8 ± 10.6 years, the duration of diabetes was 14.4 ± 8.4 years, and the duration of insulin therapy was 7.5 ± 6.9 years. Since the intervention was aimed at weight loss, all patients took an incretin-type drug - Liraglutid (Victoza). Five patients additionally took a sugar-lowering drug, a SGLT2i inhibitor, which helps kidneys to remove glucose.
Figure 6. Results of continuous monitoring of glycaemia after 6 weeks of pharmacotherapy de-intensification and complete insulin withdrawal.

As a result, a decrease in BMI from 34.1 ± 5.6 to 29.0 ± 4.1, \( p = 0.005 \), and also HBA1C were reduced from 8.5 ± 1.3 to 6.9 ± 0.6\%, \( p = 0.0002 \). This led to a significant improvement in the metabolic state of patients and allowed the withdrawal of insulin therapy. A positive correlation between CV and the average amplitude of glycaemic fluctuations (MAGE) was noted: CGM records showed a significant decrease in CV from 27.0 ± 8.0\% to 20.0 ± 6.0\%, \( p = 0.004 \); MAGE decreased from 82.9 ± 30.6 to 64.8 ± 23.4 mg\%, \( p = 0.002 \); standard variation is from 48.6 ± 18.4 mg\% to 31.5 ± 11.3 mg\%, \( p <0.001 \).

To identify the most informative index in CGM, which correlates reliably with restoration of insulin secretion and function, we studied the data of continuous monitoring of a large number of patients with T2DM from 2010 to 2017. The main CGM indices were compared before and after metabolic recovery. CGM records were evaluated using the EASY - GV program.

An analysis of the data monitoring showed that in patients with T2DM metabolic recovery and "excommunication" from insulin were accompanied by a significant decrease in all CGM parameters reflecting glucose variability (figure 7).
Figure 7. Parameters of glycaemia before and after insulin withdrawal.

No changes in hypoglycemia indices were detected. A significant decrease in MAGE and CV was observed before and after insulin withdrawal, as well as their strong positive correlation with $r = 0.7$ (figure 8).

Figure 8. MAGE and CV before and after insulin withdrawal.

CGM monitoring allowed us to come to the following conclusion: apparently, in patients with T2DM the coefficient of variability is an easily accessible and most informative index confirming the restoration of functional abilities and secretion of endogenous insulin through metabolic recovery.
Thus, CGM has become the “gold standard” tool for the latest therapeutic approaches in T2DM [17].

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