THE METHODOLOGY OF GLUCOSE MONITORING IN TYPE 2 DIABETES MELLITUS

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Abstract

Type 2 diabetes is a chronic disease and maintaining a tight glycemic control is essential to prevent both microvascular and macrovascular complications, as demonstrated in previous studies. It is essential to monitor the glucose levels in order to achieve the targets. The blood glucose monitoring can be done by different methods: glycated haemoglobin A1c, self-monitoring of blood glucose (before and after meals) with a glucometer and continuous glucose monitoring with a system that measures interstitial glucose concentrations. Even though glycated haemoglobin A1c is considered the "gold standard" of diabetes care, it does not provide complete information about the magnitude of the glycemic disequilibrium. Therefore the self-monitoring and continuous monitoring of blood glucose are considered an important adjunct for achieving and maintaining optimal glycemic control. The three methods of assessing glycemic control: HbA1c, SMBG and CGMS provide distinct but at the same time complementary information,

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The optimal glycemic control is difficult to obtain in daily practice, despite the therapeutic progresses. This can be achieved by a multi-factorial approach of the diabetic person that includes optimizing lifestyle, intensive and early pharmacotherapy, continuous education, monitoring and periodical assessment [1-3]. Intensive pharmacotherapy aims at reaching the glycemic objectives by a permanent adaptation, adjustment and individualization of the therapy, which is impossible to achieve without a careful self-monitoring and control [4,5]. Glycemic values monitoring is essential in order to reach the glycemic objective. The blood glucose monitoring can be done by different methods: determining the glycated haemoglobin A1c (HbA1c), self-monitoring of blood glucose (before and after meals) (SMBG) with a glucometer and with the use of a continuous glucose monitoring system (CGMS).

HbA1c is considered the golden standard in the management of type 2 diabetes mellitus (T2DM). It is part of the glycemic objectives and mentioned in all the guidelines and clinical recommendations for the management of T2DM [5-8]. Several studies proved that increased HbA1c values are associated with increased risk of T2DM specific complications, and lowering HbA1c leads to a decreased risk for micro and macrovascular complications [2,9-15]. It represents the average of the exposure, retrospectively, for the last 2-3 months, thus assessing the glycaemic control for a long period, but does not offer information about the daily glycaemic values and, therefore, there is no immediate feed-back to the patient regarding the therapeutic or nutritional decision. Also, HbA1c does not offer information regarding the amplitude of glycaemic variability (frequency and magnitude of the glycaemic excursions) to which the patient is exposed daily [16]. Approximately 50% of the HbA1c value is determined by the 1 month glycaemia preceding the measurement, 25% from 60 to 120 days prior to measurement, and 25% from 60 to 120 days prior to the dosage [17]. There are over 30 available methods for the determination of HbA1c, with a great variety of the reference intervals [18]. This is the reason why The National Glycohemoglobin Standardization Program, NPSP [6,19] has been created. A rapid HbA1c assay (point-of-care testing) is also available, giving patients and physicians immediate feedback and allowing to make timely therapy changes. Several medical conditions could interfere with the value of HbA1c (liver diseases, kidney diseases, hemoglobin disturbances, blood transfusions, pregnancy, hemolythic anemia, iron deficiency anemia, hypertriglyceridemia, hyperbilirubinemia, uremia, some

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drugs, alcohol abuse etc.) [19]. It is recommended to test HbA1c twice a year for the patients who achieved glycaemic objectives and four times per year in therapeutically not-controlled cases or when change of therapy is needed [8].

Real-time measurement of the blood glucose values is essential to reach and maintain glycaemic control and therefore to reduce specific complications. It comes to complete the information offered by the HbA1c. The most accessible and frequently used method is self-monitoring blood glucose (SMBG) with a glucometer and it is based on glucose dosing in capillary blood. A large variety of glucometers exist on the market and their use should be with an emphasis on accuracy of the measurement and qualitative standard. Generally, glucometer-obtained results are not so precise as those provided by lab methods, but are far more accurate than the old color-reaction methods. Introduction of the SMBG represented a milestone in diabetes management, practically, the therapeutic/nutritional decision has been transferred from the physician to the patient, who managed to take control of his own disease. Glucose measurement is performed in real time and offers information on possible hyper- or hypoglycemia. The patient is able to take immediate therapeutic decisions (pharmacological, nutritional, physical activity related, stress etc.), thus practicing a more efficient management of the disease [20-23]. SMBG also offers information about the glycemic fluctuations. There is the possibility that the clinicians download data from blood glucose meters using proprietary software and cables. The programs can be installed on individual computers or networked to several computers, and comprehensive reports can be both printed and saved. If patients use these programs at home, reports can be e-mailed to their clinicians for review. Glucometer capability is continuously being enhanced. The newest models allow patients to program their insulin to-carbohydrate ratio, correction factor, and target blood glucose level into the meter. This information enables the glucometer to recommend the next insulin dose based on blood glucose level and carbohydrate intake. Also, it recognizes patterns of hypo- or hyperglycemia and alerts the user to them. Nowadays, there are smartphone-enhanced glucometers, so blood glucose data can be downloaded to a computer without the need of additional software/cables [24]. Including self-monitoring as part of the multifactorial strategy in diabetes management leads to a significant improvement of HbA1c. Data from a large epidemiological study show SMBG in T2DM patients decreased by over 6.5 year the diabetes related morbidity and any-cause mortality [25]. Training is crucial for the self-monitoring technique, its usefulness and importance, the ability to use data in adjusting therapy (pharmacotherapy, nutritional therapy, and physical exercise) in order to achieve therapeutical objectives [23,26]. The frequency and schedule of SMBG depend on several factors such as glycemic level control, therapeutic strategy (conventional/intensive), individual and socio-economical factors. International guidelines recommend at least 3 daily of preprandial capillary blood glucose measurements for patients with intensive insulin therapy or insulin pump carriers, in other cases the frequency of SMBG should be individualized depending on the treatment scheme and glycemic level control. Postprandial monitoring is recommended for cardiovascular prevention [27]. In case of pregnant diabetic women the timing of SMBG should be individuated, as well [8,28].

There is a correlation between HbA1c and the average of plasma glucose level according to data provided by international ADAG trial (A1C-Derived Average Glucose) (Table I) [8]. This correlation applies also to glycemia determined by self-monitoring or continuous glucose monitoring [8].

Table I. Correlation between HbA1c and average glucose [8].

A1c (%)	Plasma glucose average level (mg/dl)
6	126
7	154
8	183
9	212
10	240
11	269
12	298

Continuous glucose monitoring from the interstitial fluid is a new technical method developed and applied relatively recently, that provides a full picture of the glucose profile with or without the possibility of displaying real time values of glucose [26,29,30]. It offers the possibility to evaluate the pharmacotherapy, nutritional therapy, physical activity, education and adhesion to therapy and therefore to have a major contribution at improving glycemic control.

In the setting of clinical research, this method proved to be extremely useful. These systems can use invasive measurements, minimally invasive or non-invasive techniques [31-33]. In steady glycemic conditions, the level of glycemia is similar to the glucose from interstitial fluid. But, during rapid exchange of glycemic values, the changes at the interstitial fluid level occur with a certain delay comparing to the venous blood, named lag period, whose time could extend up to 30 min. Therefore this type of glucose monitoring is not entirely identical to the glycemic level, but the information provided is extremely helpful because it offer the ability to appreciate of the glycemic tendency and to act accordingly [34]. It also provides a more comprehensive image over the development of the disease and the treatment and it motivates the DM patients to maintain a glycemic control as tight as possible [26,35].

The minimal-invasive systems have the widest use. These systems imply a sensor implanted in subcutaneous tissue level, most frequently at the abdominal level (also possible at thigh, buttock, arm levels) and allow glucose dosing from the interstitial fluid. The implantable sensor may work several days depending on the system used (3-7 days) and records a value of glucose values between 40

and 400 mg/dl at every 5 min, a total of 288 values in 24 hours. Data recorded during monitoring days are stored at a monitor level and then are downloaded and visualized on the computer as graphics, using special software (fig. 1).

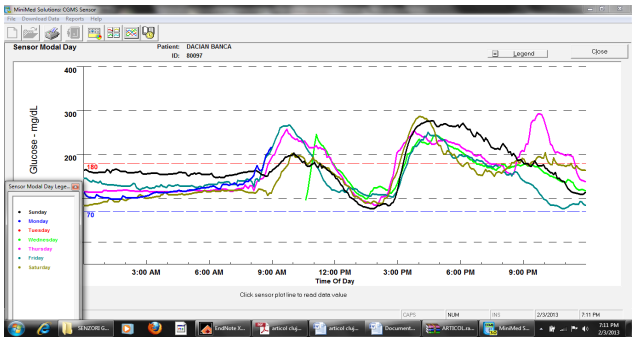

Figure 1. Aspect of downloaded sensor modal day data (personal archive).

The sensor through its enzymatic load (glucose-oxydasis), assesses glucose level in the interstitial fluid and generates electrical impulses later transformed and stored as glycemic values. SMBG is mandatory during the days of continuous glucose monitoring, 3-4 measurements are needed and their values are inserted in the CMCG, that serves as system calibration [36,37].

Indications and benefits of CGMS usage in medical practice [31,36,38-41]:

- To evaluate glycemic variability and fluctuation over 24-72 hours, to calculate the glucose average amplitude (MAGE, mean amplitude of glucose excursions);
- To record the real glycemic profile over a 1, 3, 5 or 7 day period in a much more complete manner compared to SMBG;
- To assess the influence of lifestyle (alimentation, physical activity, stress) and pharmacotherapy over glycemic control;
- To identify hypoglycemia, especially the nocturnal and unawareness phenomena;
- To identify postprandial hyperglycemia and to correct them by adopting the appropriate therapeutical strategies, leading to an improved HbA1c;
- The possibility to adjust insulin doses quickly;
- To assess the glycemic status in persons with brittle diabetes;
- To reveal phenomena such as "dawn" and "extended dawn";
- To evaluate therapeutic efficiency in a timely manner;
- To assess therapeutic efficiency and adaptation of the insulin regimen in insulin pump carriers;
- To assess the effects of behavioral changes on the glycemic profile;
- To evaluate the optimal period between the administration of different insulin preparations and alimentation, very important in case of diabetical gastroparesis;
- To evaluate the glycemic profile in diabetic individuals after pancreas transplant, pancreatic islands transplant, admitted to ICU or during surgical interventions;
- To evaluate the glycemic control in diabetic individuals with erythropoietin treatment, an agent that influences HbA1c value;
- To use the results for education purposes to increase treatment adhesion and lifestyle modification for an optimum glycemic control;
- To use the results for research purposes;
- To assess glycemic status in individuals with insulinoma, glycogenoses;
- To assess glycemic status in overweight/obese individuals;
- To assess glycemic status in individuals being in critical status or postsurgery.

Conclusions

The three methods of assesing glycemic control, HbA1c, SMBG and CGMS provide distinct information, yet complementary at the same time. HbA1c does not equally reflect the glycemic values over the three months that forego its determination. Also, its value is not influenced by the lability of glycemic balance. HbA1c assesses the average glycemic exposure in time without being able to differentiate between preprandial and postprandial glycemia, possible hypo and hyper glycemia. SMBG comes to fill in the information received in real-time. This method is able to identify both hypoglycemic and hyperglycemic episodes allowing immediate therapeutic decisions and therefore a glycemic balance closer to normal.

Introduction of CGMS in the assessment of the glycemic status represents a great technological advance. This glucose monitoring method clears glycemic balance abnormalities in an otherwise impossible to obtain manner, evaluating both therapeutic efficiency and glycemic control. Even if CGM systems are far from being implemented at a large scale in current practice, they are about to change the diabetes management by providing an optimal glycemic control.

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