History of glucose monitoring: past, present, future

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Abstract

New technologies in diabetes care are developing dynamically in recent years. The article presents a historical outline of the methods of glucose measurement and current and developing glucose monitoring technologies.

Key words: glucose monitoring, glucose meters, CGM, FGM, diabetes

Introduction

Diabetes mellitus (DM) has become a first noninfectious global epidemic that affects approximately 425 million people worldwide. That equals to 8,8% of the population aged 20–79 years. According to the International Diabetes Federation, the number of patients is still increasing at an extremely rapid rate [1].

Type 1 diabetes mellitus, also known as insulin-dependent diabetes mellitus, is a chronic immune-mediated disease that is characterized by destruction of loss of β cells in genetically susceptible subjects. Type 2 diabetes is usually the result of insulin resistance and related to overweight or obesity. Regardless of the particular pathophysiology of an individual's diabetes, the characteristic of the vast majority of diabetes is insufficient insulin secretion and hyperglycemia resulting from β-cell destruction or dysfunction. The uncontrolled disease and chronic hyperglycemia lead to serious microvascular or macrovascular complications over

time such as cardiovascular disease, blindness, neuropathy and nephropathy that are mostly irreversible [2].

Diabetes has been known for almost two thousand years. In 150 AD the Greek physician Aretaeus used the term "diabetes" and described classical symptoms of the disease:

- constant thirst,
- excessive urination,
- loss of weight [3].

In that time it was an incurable disease and patients have died within a few years after the diagnosis of the disease. The pathophysiology of DM remained unknown but further discoveries have explained the pathophysiology of the disease better and better:

- Thomas Willis, 1674 - discovery the sweetness of urine,
- Matthew Dobson, 1775 - an identification the causes of the sweet taste of urine,
- John Rollo, 1797 - the discovery that the amount of sugar excreted in urine depends on the type of food,
- Paul Langerhans, 1869 - the discovery of the islet cells of the pancreas,
- Naunyn, Minkowski and Mering, 1889 - the discovery of a role for the pancreas in diabetes [4].

These findings enabled the revolution in diabetes therapy - the discovery of insulin by Banting, Best, and Collip, which was one of the most important events in the history of medicine. The first injection of a crude beef pancreatic extract was given to 14-year-old Leonard Thompson on January 11, 1922. The discovery of insulin was awarded the Nobel Prize in Medicine in 1923 [4].

Monitoring of glucose level

Diabetes management requires monitoring of glucose level and adequate insulin dosing depending on diet, physical activities and many other factors affecting blood glycemia.

The first method allowing for the control of glucose level was urine test and urine test strips. Nevertheless, both had poor results in managing blood glucose level and led to early severe vascular complications [5].

The first blood glucose test strip, the Dextrostix, utilizing the glucose oxidase-peroxidase system developed in 1965 was a more reliable diagnostic tool. Although the visually monitored blood glucose test strips were widely used, they had significant disadvantages such as color fading and highly significant visual variations in the assessment of colors across the range of glucose concentrations [6,7].

Self-monitoring of blood glucose

The development of electric glucose meters has given definitely more accurate results than strip test papers. The first portable glucose meter, Ames Reflectance Metering, was created in the late 1960s and became available in 1970. Since then self-monitoring of blood glucose (SMBG) has become possible. Self-monitoring blood glucose meters are portable devices that measure blood glucose concentration on a drop of capillary blood using finger-stick blood

samples and test strips. Since the meters and reagent strips costs have reduced, SMBG has become the most widely used method for measuring blood glucose levels. Nowadays, SMBG is an essential tool in diabetes self-managing. By enabling patients to monitor their blood glucose levels, significantly improved glycaemic control and diabetes management among diabetics have been observed [7].

Over the past 4 decades, enormous progress has been made in glucose meters technology. The size of SGBM meters has been reduced, and its accuracy has been improved. Many meters now have more advanced data-handling capabilities and additional features to record daily doses of insulin, intake of carbohydrates and workout history.

However, pain associated with the finger prick is one of the biggest limitations of this method. It might be frightening for some patient and it makes patients less likely to control blood glucose levels. Another weakness of this method is insufficient sampling frequency. The SGBM provides only the current capillary blood glucose concentration without information about the glucose trend. Intermittent capillary glucose testing with three to four finger-stick tests providing a snapshot of day-to-day glucose control.

Glycated hemoglobin

Glycated hemoglobin, measured as total HbA1c, was first introduced into clinical laboratories for diabetes monitoring around 1977. In contrast to SGBM, HbA1c reflects average blood glucose level during the preceding 120 days and it has gained high acceptance as an index for assessing the risk of complications and as a prognosis indicator for the success of treatment of diabetes. Nevertheless, none of these methods provides information about major changes in glucose level such as hypoglycemia and hyperglycemia during a day. Better long-term diabetes control resulting in a reduction in HbA1c is associated with decreases complications. However, tight glycemic control is associated with the risk of hypoglycemia remains the most feared complication of insulin therapy since it was described, which limits the possibility of intensification of treatment (8–10).

Continuous Glucose Monitoring

The introduction of real-time continuous glucose monitoring (CGM) that measures glucose levels continuously is another breakthrough in diabetes care. Typically CGM comprises glucose-sensing device inserted in the abdomen or on the arm, electrochemically measuring glucose levels in subcutaneous tissues every 1–5 min. The sensor provides information about interstitial glucose that is transmitted and visible on the monitor. Moreover CGM-based treatment almost eliminates the need for finger-sticks, it requires finger-sticks just for a calibration procedure, usually only twice a day.

The first successfully commercialized CGM sensor, The Guardian RT System (Medtronic Minimed), got FDA approval in 1999 [8]. Early models of CGM (professional CGM) provided a retrospectively summary of glycaemic control and were readable only by a specialist. Currently available CGM devices are available for diabetic self-management at home, they offer real-time monitoring, provide graphs of glucose trends and alerts to impending hypoglycemia and hyperglycemia events.

Flash Glucose Monitoring

Flash glucose monitoring system (FGM) measure the glucose concentrations in the interstitial fluid without any calibration requirements. It is the unique and newest method of glucose monitoring because, in contrast to the available CGM systems which still require calibration using capillary blood glucose readings, the FGM system is factory calibrated. Finger-stick testing is not required to calibrate system by the user or to confirm the data's accuracy.

As a result of the time required for the movement of glucose from the vascular to the ISF space physiologic time lag (or equilibration time) which has been estimated to be 5-6 minutes in healthy adults, finger-stick checks may be needed only in some situations when glucose levels are rapidly changing, or when symptoms don't match the system's readings [9]. FGM is seen as a hybrid between standard glucometers and continuous glucose monitoring systems. Reduced cost and factory calibration are two of the most innovative features of FGM.

Flash glucose monitoring sensor is inserted on a patient's upper arm. The scannable sensor transmits an instantaneous glucose level and trend graph to the separate reader device when it is swiped close to the sensor. FGM requires the patient to place the receiver close to the sensor for data visualization, so a permanent connection to an external device isn't possible. It does not provide continuous glucose monitoring, trend data in real-time, and does not have hypoglycemia or hyperglycemia alarms for real-time blood sugars. The glucose level in unknown when it's not manually tested, e.g. during the night, however the sensor can be scanned by someone else whiles patient is asleep [2,10,11].

Flash glucose monitoring systems is actually provided by the only one company, Abbott Diabetes Care. Their FGM device, FreeStyle Libre, was introduced in 2014, and it was approved by the FDA in September 2017. The first-generation of FreeStyle Libre sensors have been approved for wear for 10 days, the second-generation that can be worn for 14-days has been recently approved. The newer generation has also lower mean absolute relative difference (MARD) which means it is more accurate (9,7 vs 9,4%) [12–14].

Closed-loop

Closed-loop control systems enable the automatic delivery of insulin and glucagon. CGM systems and insulin pumps are the pillars of this artificial pancreas system. Real-time CGM can control insulin delivery from an insulin pump.

The Medtronic MiniMed 670G System is the first FDA hybrid closed loop system which was approved on September 28, 2016, for users aged 14 years and older, and has been recently approved in users under seven years of age. The device monitors glucose level and automatically adjusts the delivery of long-acting or basal insulin, so there is no need for any manual control of the device. This device consists of a continuous glucose monitor that measures the user's glucose levels for up to seven days, an insulin pump that delivers insulin to the user, and a glucose meter used to calibrate the CGM [15].

Currently, limited results suggest that the usage of a fully automated closed-loop insulin delivery system in patients with diabetes in the general ward is as safe and effective as standard subcutaneous insulin therapy. The significant reduction in HbA1c level, hyperglycemia, and hypoglycemia events confirm the effectiveness of the device in self-glucose management [16–20].

Discussion

In the field of diabetes we observe significant technological developments over a relatively short period of time. The latest devices for measuring glucose level presented in the article are significant support in the daily routine of diabetics. Unfortunately, due to high costs and still low dissemination of these modern techniques, they remain available only to a small group of patients. Nevertheless, the development in diabetology management goes in the direction of advanced autonomous devices, which in the future will allow for a significant improvement in the state of health and quality of life of diabetic patients.

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