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Review of present method of glucose from human blood and body fluids assessment

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ABSTRACT

the work has been aimed to create an overview of available and used methods and ways to determine the concentration of glucose in body fluids, especially from a technical point of view. It also provides an overview of the clinical features of these methods. The survey found that today's market offers a large number of options and approaches to the issue. There are accurate reference laboratory methods, self-monitoring methods for measuring glucose levels using glucometers, or continuous methods for daily monitoring of blood glucose trends and for insulin pump control. However, it must not be forgotten that the development of full closure of feedback is still not complete today. Individual methods cannot always be compared with each other, precisely because of the focus and the use of these methods. Choosing the right method of blood glucose levels in the body measuring can help patients to manage their diabetes mellitus. The methods listed in the overview are divided in terms of measurement continuity and further according to the invasiveness of the method. Finally, the issues of accuracy in the detection of glycaemia variability and the possibility of further development of these methods are discussed, as it is clear from the survey that the development is focused mainly on continuous methods improving that get to the forefront and also on developing a biosensor that is purely non-invasive and continuous.

1. Introduction

In the last decades due to many factors, such as changes in eating habits or in the physical activity, the increase of pathologies related to the incorrect amount of glucose circulating in the blood together with new findings on disease related to the same factor have pushed the research to study innovative solutions for the glucose measurement. The disease associated with incorrect blood glucose levels is called Diabetes Mellitus (DM) occurring in several forms: type 1 DM, type 2 DM, moreover, there are other forms of DM, included the gestational DM and more specific types of diabetes caused, for example, by Monogenic syndromes of diabetes, exocrine pancreatic diseases; a serious long-term condition that ranks 10th most common causes of death in the world. Type 2 DM is more common and accounts for approximately 90% of the total number of diabetics, this number of patients is continually growing up (Saeedi et al., 2019). 374 million people are at a greater risk of developing of this type of disease. Diabetes of the first type is more common in children and adolescents; more than 1.1 million children and adolescents are living with type 1 diabetes (IDF, 2020). The two most common type of diabetes are related to the inability of the pancreas to produce insulin (DM1) or reduced tissue sensitivity to insulin (DM2); in both cases the carbohydrate metabolism is impaired, so it is very important to check the blood glucose levels. The measured of glucose concentration value is an important indicator of the human body condition: according to the value obtained, appropriate procedures may be provided to adjust the blood glucose level in order to ensure the internal homeostasis of the organism. The World Health Organization (WHO) has identified DM as an epidemic due to the rapid growth of sick individuals (Lin et al., 2019) (WHO - Diabetes, 2021). Statistics of 2019 suggest that Diabetes Mellitus (a combination of DM 1 and DM 2) affects 463 million people, 20–79 years of age, from the world's population, with 46% of people with diabetes undiagnosed (Gray et al., 2018) (Cho

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et al., 2018) (Vashist et al., 2011). In 2019, the costs associated with Diabetes Mellitus were estimated at $ 760 billion (IDF, 2020). The most common diabetes-related complications are ischemic heart diseases, strokes, blindness, end-stage renal diseases, and lower limb amputations (Leasher et al., 2016) (Ravizza et al., 2019). Therefore, the control of blood glucose levels to reduce the patient's risk of developing these complications is an important part of diabetes management (CADTH, 2010).

Most of the glucose monitoring articles available today are focused mainly on the medical applications of glucose measurement achievable by these specific sensors, with particular reference to the statistical analysis of errors and to the measurement reliability. On the other hand, there are very few review works that systematically examine the principles of glucose detection and that analyze deeper the mechanism of the enzymes-based reaction: the influence of interferents or the use of a detailed reaction mechanism on the reliability of measurements it is not mentioned indeed in the available literature works, that in general do not provide neither information on the needing of such sensors for microfluidic solutions or detailed aspects on alternative methods of measuring glucose.

In the current research scenario, there are some specific articles describing new principles for glucose monitoring that, if implemented, would significantly improve the performances of dedicated devices. In fact, there are far fewer publications about the principles that are applied and in most of extensive reviews often early publications on glucose measurements and glucose sensors are not mentioned. Even if these methods could be considered technically outdated, it is important to highlight that without this information a reliable glucose sensor cannot be developed. Moreover, these aspects represent an important issue for the commercial industry, considering that glucose sensors belong to an area with a daily turnover of millions of US dollars.

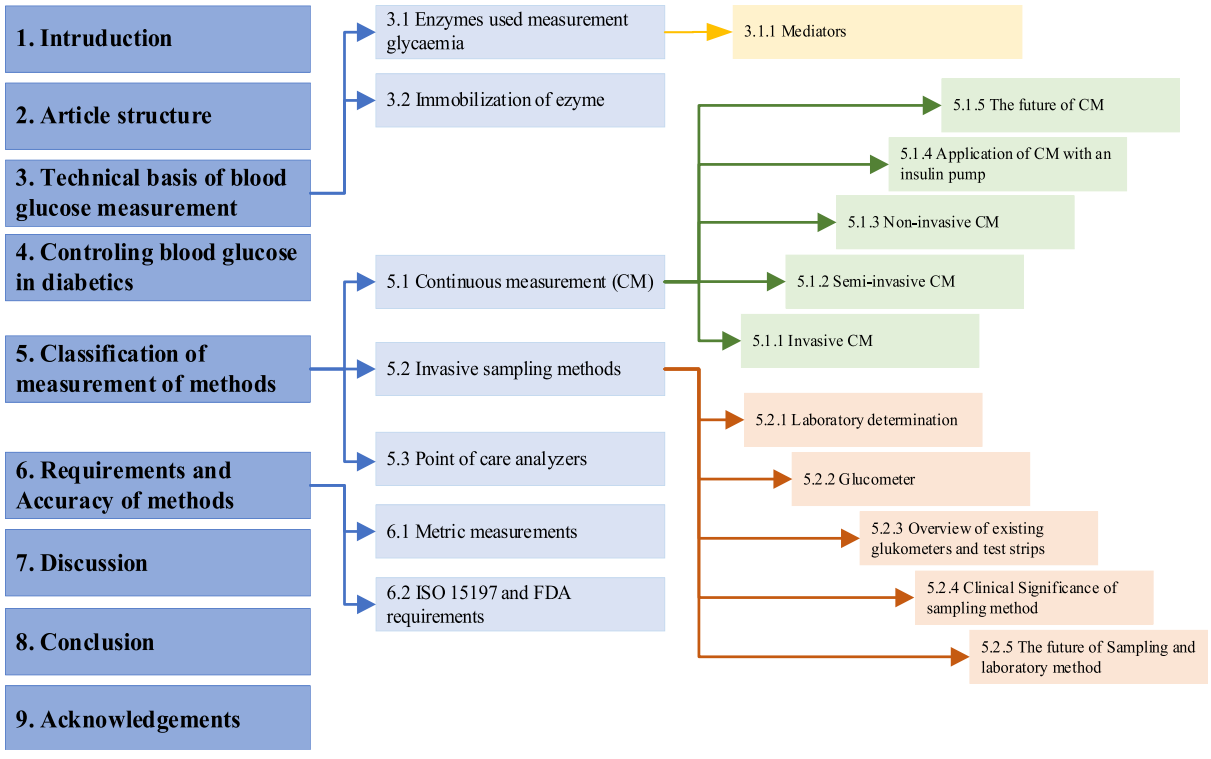
DM's pathology represents one of the most common among the populations that necessitate of specific systems and devices for the glucose monitoring, laboratory test and performing oral glycaemic tolerance test (OGTT). There are many methods to determine blood glucose levels that can in generally classified on the basis of the adopted continuous or non-continuous techniques which is further subdivided in terms of invasiveness. Anyway, the most of these, rely on a chemical reaction between the glucose and a specific reagent that produces a measurable signal, so the amplitude of the generated signal is based on the concentration of the acting components. In most the cases, a biosensor is used to measure blood glucose levels. In recent years huge progresses have been done in the development of glucose sensors and those are nowadays commercially available for a wide range of applications and users, such as for biochemical laboratories or for subjects affected by diabetes mellitus, that can easily use diagnostic strips or continuous glucose sensors. As the field of development and production of biosensors, especially for the analysis of glucose concentration, is a trend nowadays and occupies a large place on the market, we dedicate the own chapter 3 Technical basis of blood glucose measurement - biosensor to the issue of biosensors.

2. Article structure

This work aims to provide a comprehensive information about glucose measurement methods with a particular reference to the specific techniques of glucose biosensors: all the methods and techniques mentioned are detailed highlighting working principles and main field of applications to give a complete overview on these systems.

The basis of the submitted review was the selection of suitable databases (in particular Scopus, Web of Science, PubMed, Engineering Village). The combination of technical and medical literature provided a good basis for a comprehensive review. Full papers, including original contributions in journals, conference proceedings, and a capitol from

Table 1
Article structure.



books were used. Only English language papers were used.

The exact structure of the article is shown in Table 1. The article is structured as follows: Chapter 3 Technical basis of blood glucose measurement biosensor deals with the technical design of the biosensor, as it is currently the basic element for glucose control. Chapter 4 Controlling blood glucose in diabetics provides basic information on glycaemia control and diabetes mellitus. Chapter 5 Classification of measurement methods shows the division of methods, according to which the other chapters are arranged. At the end, chapters are given, where information related to the presented topic can be found.

3. Technical basis of blood glucose measurement - biosensor

The findings in this field have been so successful and effective that nowadays the glucose sensor production is one of the main financial supporters in the development of many systems in the biosensor industry up to 85% of biosensor production is targeted to glucose biosensors (Toghill and Compton, 2010). The most general basis is the function of the biosensor in the use of natural principles in analytical practice. The functioning of a biosensor is generally based on the separation of the substance to be analyzed, as for example the glucose, that is transferred to the bioactive layer and is connected to a physiochemical transducer (Jędrzak et al., 2019) (Rernglit et al., 2019). This can convert the concentration of the analyzed substance into a proportional electrical quantity, thus generating a signal during time that reveals the trend of glucose level. According to the measurement technique, we distinguish several groups, eg amperometric, potentiometric, conductometric, etc. Amperometry is a method based on measuring a signal, which arises from the flow of electrons exchanged in an electrochemical reaction at a constant electrode voltage. The current is directly proportional to the concentration of the studied substance. Potentiometry is based on the change in potential induced by the collected charge at the interface of the electrode with the solution and conductometric biosensors use the ability of electrolytes to conduct electricity.

It can, therefore, be divided into a part of recognition elements (receptors, enzymes, antibodies) separating the analyzed molecules and parts of the converter. The task of transducers is to convert information from a chemical reaction to an electrical signal or to another type of signal that the transducer can use electrochemical, optical, calorimetric method (Yoo and Lee, 2010). In practice, we can most often meet with electrochemical converters. In the field of biosensors for glycaemic measurement, mainly three generations of biosensors can be identified: a general scheme of the adopted principle is shown in the following figure Fig. 1 The overview of biosensor generations (Toghill and Compton, 2010) where an explanation of the respective generations in terms of reactions is given below in the enzyme section (Hatada et al., 2018).

The biosensors of first-generation were based on the use of natural oxygen and recorded the amount of hydrogen peroxide produced. The main drawback was in the fact that amperometric measurements require high operational potential for proper selectivity and a so-called "oxygen deficit", caused by the limited solubility of oxygen in biological substances, occurred in these sensors (Yoo and Lee, 2010). The biosensors of second-generation can be described as first-generation biosensors with a mechanism to compensate errors. They were introduced mediators as oxidative reagents. Mediators are used as electron acceptors to transfer free electrons from the enzyme to the working electrode. Oxygen is thus eliminated as an oxidizing agent (Scheller et al., 1991).The biosensors of third generation utilize electron transfer without a mediator, i.e. a direct transfer using complex conductive materials. This generation of sensors has begun to evolve towards implantable, needle-based continuous sensing devices and excel in their selectivity (Horaguchi et al., 2014).

There are also non-enzymatic biosensors. These sensors could represent the fourth generation of biosensors, and they are based on direct glucose oxidation in the analyzed sample by electrodes (Hwang et al., 2018). The most common measurement principle is the fixed potential amperometric method. The greatest obstacle to this method is the blood glucose concentration, which should range from 2 to 10 mmol/l (Toghill and Compton, 2010). Promsuwan et al. disclose a novel non-enzymatic glucose sensor based on flow injection, which uses an electrode modified by a nanocomposite of mulled-wall carbon nanotubes coated with nanoparticles of palladium and graphene nanoparticles (Promsuwan et al., 2019). The most commonly used electrodes are metals such as platinum and gold, metal oxides $Ni(OH)_2$, RuO_2R,

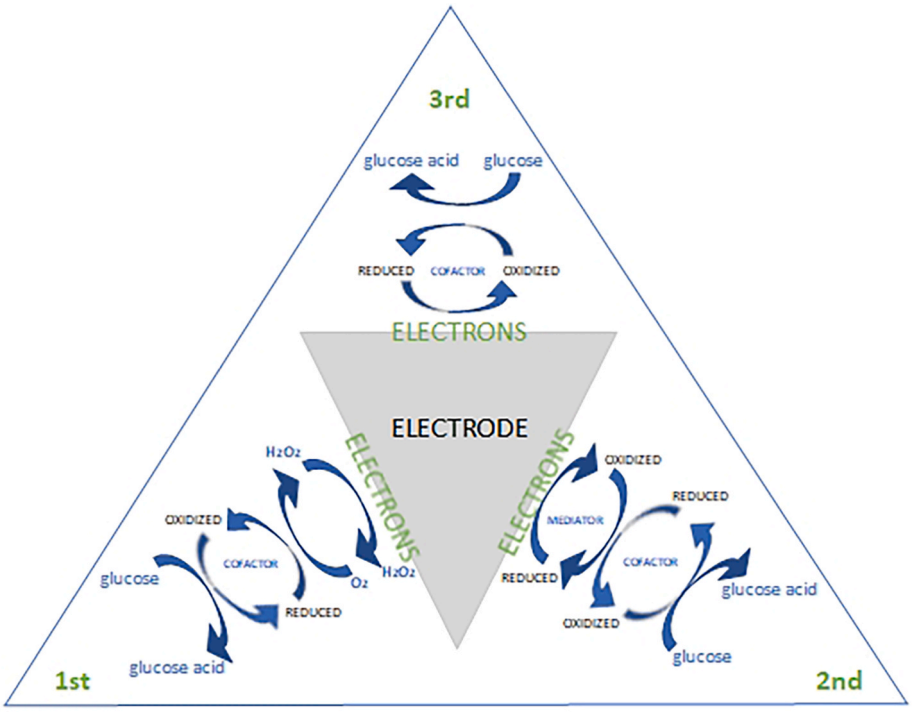


Fig. 1. The overview of biosensor generations (Toghill and Compton, 2010).

alloys PtPb, PtRu, complexes of cobalt phthalocyanine and carbon nanotubes (Toghill and Compton, 2010). The electrode geometry is also important for the definition of these sensors. The illustration Fig. 2 The principle of non-enzymatic electrodes (Toghill and Compton, 2010) shows the principle of non-enzymatic electrodes.

3.1. Electrochemical biosensors

Electrochemical biosensors belong to the oldest and still most used types of biosensors, use the electrochemical method is based on the chemical reaction of glucose, resulting in the formation of product, which is measured or disintegrates on the electrode and free electrons are formed. There is a direct proportion, in which the number of product or electrons formed corresponds with blood glucose concentration (Toghill and Compton, 2010) (Wang and Lee, 2015). In this field, enzymatic sensors, which were developed in 1962 by Clark Lyons (Clark and Lyons, 2006), has ha predominant role. Further developments in the area were provided by Updike and Hicks and are described in (Updike and Hicks, 1967). Modern enzymatic biosensors use the amperometric principle, and the commercially available ones are relatively accurate. Nowadays, electrochemical enzymatic biosensors are the most common and they occupy a large market share (Hwang et al., 2018).

The most common blood glucose concentration analysis technique used in biosensors is based on the use of the enzyme glucose oxidase (GOx) (Bankar et al., 2009) (Bollella and Gorton, 2018). Other enzymes used are glucose dehydrogenase (GD), hexokinase (HK), glucose-6-phosphate dehydrogenase (G-6-PD) (Ahn et al., 2018) (Bai et al., 2018) (Flexer and Mano, 2014) (Karter et al., 2001).

When using enzymes, it is necessary to use other substances. It is necessary to create a suitable and optimized "mixture" of these substances. The composition of this mix also affects the immobilization of the enzyme to the test strips. Immobilization techniques used, that include adsorption, crosslinking, electropolymerization, and chosen monomer, are described in the following. The reliability of biosensors is related to its lifetime, which is influenced by enzyme degradation, chemical interference or biofouling (Boudrant et al., 2020). Biosensors with enzymes and mediators are often provided with a biocompatible membrane against contamination and unwanted immune responses: the membranes are composed by lipids, polymers, and hydrogels (Kim et al., 2019) (Lopes et al., 2018) (Vashist et al., 2011).

3.2. Enzymes used measurement glycaemia

The glycemic measurements use enzymes in most casess. Enzymes are used to specifically detect blood glucose and to catalyze the reaction (Heller and Feldman, 2008). Enzymes provide the necessary chemical reactions and due to these reactions, a colored product, free electrons, or hydrogen peroxide is formed, which is further detected and analyzed (Vashist et al., 2011). The enzymes reported in the following paragraph react with β-glucose but differ in cosubstrats, the Michaelis constant, the glucose selectivity or the redox potential (Heller and Feldman, 2008)

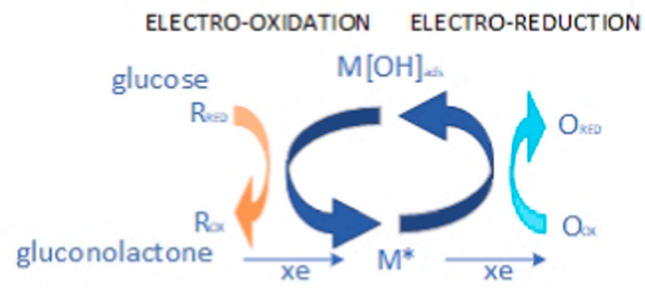


Fig. 2. The principle of non-enzymatic electrodes (Toghill and Compton, 2010).

(Hermanson, 2013). Further specifications of the enzyme use are given in the relevant chapters.

3.2.1. Glucose oxidase enzyme

GOx is a classical enzyme used in biosensors and it is used for its high selectivity for glucose, stability and relatively low cost (Mano, 2019). GOx isolated by Muller in 1928, is obtained by isolation from Asperillus niger, a dimeric protein (Muller, 1928). It contains the redox cofactor flavinadenine dinucleotide (FAD), which is located in the reactive zone (Yoshida et al., 2015). The cofactor is used for the uptake of electron and for its oxidation oxidizing substances are used, mostly O2 (Vashist et al., 2011) (Yoo and Lee, 2010).

The basic concept of using GOx is illustrated by the following reaction scheme:

$$Glucose + (GOx - FAD^{+}) \rightarrow Glucolactone + (GOx - FADH_2)$$

$$(GOx - FADH_2) + O_2 \rightarrow (GOx - FAD) + H_2O_2$$

Hydrogen peroxide is then oxidized at the electrode while releasing 2 electrons:

$$H_2O_2 \rightarrow 2H^{+} + O_2 + 2e$$

The peroxide decomposition is performed by feeding 0.6 V to the sample to be analyzed (Toghill and Compton, 2010). During the chemical reaction, glucose and dissolved oxygen are consumed. The transfer of electrons to the electrode is mediated by a specific mediator. To avoid direct transmission of electrons from the reaction site to the electrode, a layer of protein forms an inner barrier (Toghill and Compton, 2010) (Vashist et al., 2011).

Another possibility is to use GOx and the enzyme poroxidase to form a colored compound, which is analyzed by absorbance. This use is mainly used in laboratory conditions. The basic application of this principle is shown in the following diagram (Blanco-López et al., 2020).

$$glucose + O_2 + H_2O \xrightarrow{glucoseoxidase} gluconolactone + H_2O_2$$

$$H_2O_2 + colorless\ chromogen \xrightarrow{peroxidase} H_2O + \ color\ product$$

3.2.2. Hexokinase

The hexokinase enzyme is used for the reference method using spectrophotometry, particularly in laboratories (Yoo and Lee, 2010). Hexokinase serves to phosphorylate glucose in the presence of adenosine triphosphate (ATP). The resulting glucose-6-phosphate (G6P) is oxidized to gluconate-6-phosphate by the enzyme glucose-6-phosphate dehydrogenase (G6PDH) in the presence of nicotinamide adenine dinucleotide phosphate ($NADP^{+}$) to form tinamide adenine dinucleotide phosphate (NADPH) (Slein, 1965). The main reaction principle is reported in the following:

$$Glucose + ATP \Leftrightarrow^{hexokinase} G6P + ADP$$

$$G6P + NADP^{+} \Leftrightarrow^{G6PDH} 6 - phosphogluconat + NADPH + H^{+}$$

The amount of NADPH formed is then determined spectrophotometrically according to its wavelength absorption 340 nm.

3.2.3. Glucose dehydrogenase

Some glucometers use the enzyme glucose dehydrogenase (GDH): its main advantage is the resistance to different levels of hemoglobin oxygen saturation. GDH is a quinoprotein using pyrroloquinoline quinone (PQQ) as a cofactor. In addition to PQQ-GDH, modifications of FAD-GDH or NAD-GDH are also used.

It also belongs to the family of dimeric enzymes and consists of two identical protein monomers. Three calcium ions and a PQQ molecule are bound to one monomer. The calcium ion serves to activate the cofactor and others are used to dimerize the GDH molecule (Hwang et al., 2018)

(Mori et al., 2011) (Yoo and Lee, 2010).

The mechanism of the reaction is similar to that of FAD – GOx: in this case the oxidizing agent is not O_2, but nicotinamide adenine dinucleotide (NAD). The reduction potential of the reaction at pH 7 is about 10.5 ± -4 mV. PQQ-GDH has the catalytic activity of both glucose and maltose and other sugars, but rarely present in patients' blood (Hwang et al., 2018) (Yoo and Lee, 2010). The basic equations when using GDH is:

$$Glucose + \text{GDH} - PQQ(ox) \rightarrow gluconolactone + \text{GDH} - PQQ(red)$$

or

$$Glucose + NAD^{+} \xrightarrow{GDH} gluconolactone + NADH$$

NADH is then oxidized at the electrode while releasing 2 electrons:

$$NADH \rightarrow NAD^{+} + H^{+} + 2e$$

or NADH spectrometry at 340 nm is used.

3.2.4. Mediators

A mediator, that can exist in both organic and inorganic forms and takes both oxidized and reduced forms, is used in these processes to transmit electrons. During enzymatic reactions, electrons are transferred to the working electrode. The mediator should have a lower redox potential compared to other active interferents present in the sample. Low potential prevents reaction with other molecules (e.g. bilirubin, uric acid) (Chaubey and Malhotra, 2002) (Nakaminami et al., 1997).

The most commonly used mediators in commercial strips include ferrocene derivatives, $Os^{2+/3+}$ complexes, fericyanide, quinine, tetracyanquinone dimethane (TCNQ) and tetrathiofulvalenes (TTF) or ferrocyanide (ferrocyanide). Ferrocene is mainly used in GOx reactions, since it is made of small molecules that, due to their size, can access the active site of GOx. They are suitable mediators especially because they do not react with oxygen, have rapid reactions with the enzyme and are stable. Mediators type $Os^{2+/3+}$ are used for strips based on PQQ - GDH and FAD - GDH. To select a suitable mediator for an amperometric biosensor, it is good to study its properties using cyclic voltammetry (Chaubey and Malhotra, 2002) (Nakaminami et al., 1997).

3.3. Immobilization of enzyme

The problem with the use of the enzyme to measure glucose concentration, is that they are soluble in water, so it is necessary to ensure their proper isolation. This problem has been solved by finding immobilization techniques by which the enzyme is attached to a given carrier. The advantages of using these techniques include, for example, repeated use of enzymes or their increased stability (Nguyen and Kim, 2017) (Yazaki et al., 2014). Immobilization of the enzyme helps to limit its mobility by physical or chemical means, while the enzyme retains catalytic activity. The immobilized enzyme can be reused in a continuous mode and is less sensitive to activators and inhibitors (Nguyen and Kim, 2017) (Yazaki et al., 2014) (Gonçalves et al., 2019). There are many enzyme immobilization methods including adsorption, crosslinking or covalent bonding. An overview of immobilization techniques is shown in the figure Fig. 3. Absorption methods include physical adsorption, electrostatic bonding, hydrophobic adsorption, layer-by-layer (LBL) deposition, electrochemical doping, or hydrophobic adsorption (Hou et al., 1998). Covalent bonds include techniques such as the activation of carboxyl groups, the activation of amino groups or the chemisorption (Karav et al., 2017) (Wang et al., 2016) (Zdarta et al., 2018). Another well-known method is to capture enzymes during electrochemical polymerization in enzyme-containing solutions. There are also methods of photopolymerization and for sol-gel process or encapsulation immobilization (Kowalewska and Jakubow, 2017).

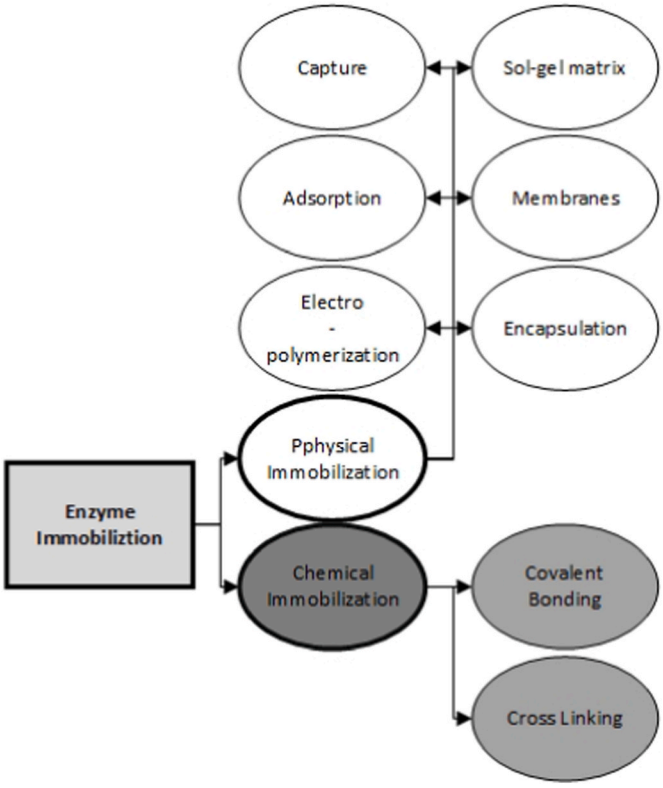


Fig. 3. The scheme of division of immobilization techniques.

4. Controlling blood glucose in diabetics

Controlling blood glucose levels throughout the day using a blood glucose meter or continuous methods of measuring blood glucose is nowadays a common practical, that is normally indicated as self-monitoring. This represents the most effective method in keeping under control the diabetes effect. This monitoring is normally used to monitor the status of a diabetic patient but it plays no role in the diagnosis of diabetes that have to be achieved with more complex techniques which are laboratory tests and OGTT. It also has its place point-of-care monitoring (POC). A great role in fighting this pathology has been given by the Diabetes Self-Management Education (DSME), a process that aims to give support and instruments to inform patients on how to control their diabetes (Norris et al., 2002) (Yoo and Lee, 2010) (Zajac et al., 2010). However, the early diagnosis of DM remains a difficult and unsolved challenge (Demitri and Zoubir, 2016) (Chamberlain et al., 2016) (Karter et al., 2001).

Capillary blood, plasma and interstitial fluid are used to measure glucose concentration. In general, plasma glucose is considered the "gold standard" and is also evaluated during laboratory diagnosis to diagnose diabetes mellitus. Glucometers most often use capillary blood and continuous methods use interstitial fluid. The target for fasting blood glucose is about 3–5.6 mmol/l while the target postprandial blood glucose is 5–7.5 mmol/l. Values below 3 mmol/l and 7 mmol/l are considered pathological and in this case the monitoring of the blood glucose levels is strictly necessary. A well-informed patient can then quickly respond to high-risk conditions and adopt therapeutic decisions to prevent further pathology that could require a hospitalization. It is important to note that the values in capillary blood, plasma and interstitial fluid are not the same (Vashist et al., 2011). The glucose dissolves in water, and since plasma has a higher water concentration than red blood cells the plasma will have a higher glucose concentration than whole blood. Capillary blood glucose values are approximately 15% lower than plasma values. A correction factor with a baseline value of

1.11 is also used to describe the relationship between plasma and whole blood in the concept of comparison with the reference method and is based on molality activity and glucose concentration in the analyzed sample. The value of 1.11 is used in cases where the concentration of water and hematocrit is normal. If a concentration violation occurs, the calculation is used 0,84/(0,93-0,22*Hct) (D'Orazio et al., 2005).

Previously, urine was standardly used for glucose analysis along with staining test strips. Today, these methods are used for screening in larger groups of people, where probable patients can be identified and risk can be prevented. However, tests based on urine analysis at the time of day cannot be considered correct for glycemic monitoring (Clarke and Foster, 2012).

In clinical practice recommendations are to monitor blood glucose levels at least 3–5 times a day in patients with type 1 diabetes and once a day in patients with type 2 diabetes for the correct pharmacological treatment (insulin or oral administration). There are no established recommendations for patients with type 2 diabetes who are receiving non-pharmacological treatment (diet, exercise) (Karter et al., 2001).

There are currently two techniques mainly used for the glycemic control (Fabris and Kovatchev, 2020) (Galindo and Aleppo, 2020) (Schweiger and Battelino, 2020): the self-monitoring blood glucose (SMBG) or continuous glucose monitoring (CGM). Many medical devices and systems have been developed to diagnose the blood glucose concentration have by several manufacturers: among these the principal ones are Abbott, Roche Diagnostics, Bayer, Minimed, Lifescan, Dexcom and Medtronic (Yoo and Lee, 2010). The development of the devices is focused mainly on their simplicity, friendliness, accuracy (Hwang et al., 2018) (Vashist et al., 2011).

An important parameter of long-term compensation is glycated hemoglobin (HbA1c), which expresses the long-term blood glucose status at 8 to 12 weeks, with an A1C calculation. The proportion of HbA1c concentration in total blood haemoglobin is considered to be a routine and most effective tool for monitoring the course of DM (The EurA1c Trial Group, 2018). The decision limits for HbA1c are given in mmol/-mol. For an adult (non-pregnant if female), the interval is 20–42 mmol/mol and for compensated diabetes, the limits are set between 43 and 53 mmol/mol (Andriankaja et al., 2019) (American Diabetes Association, 2020) (Weykamp et al., 2008). Literary data on decision limits are often different and these differences are also caused by the uncertainty of the HbA1c determination, which depends on the chosen measuring technique. Two evaluation methodologies are used: DCCT – Diabetes Control and Complication Trial (boronate chromatography; units %) and IFCC – International Federation for Clinical Chemistry and Laboratory Medicine (HPLC/MS, HPLC/CE; units mmol/mol) (Ali, 2020) (Krhač and Lovrenčić, 2019).

5. Classification of measurement methods

Among glucose sensors, a wide range of technologies are based on chemical or physical principles to determine the concentration. In

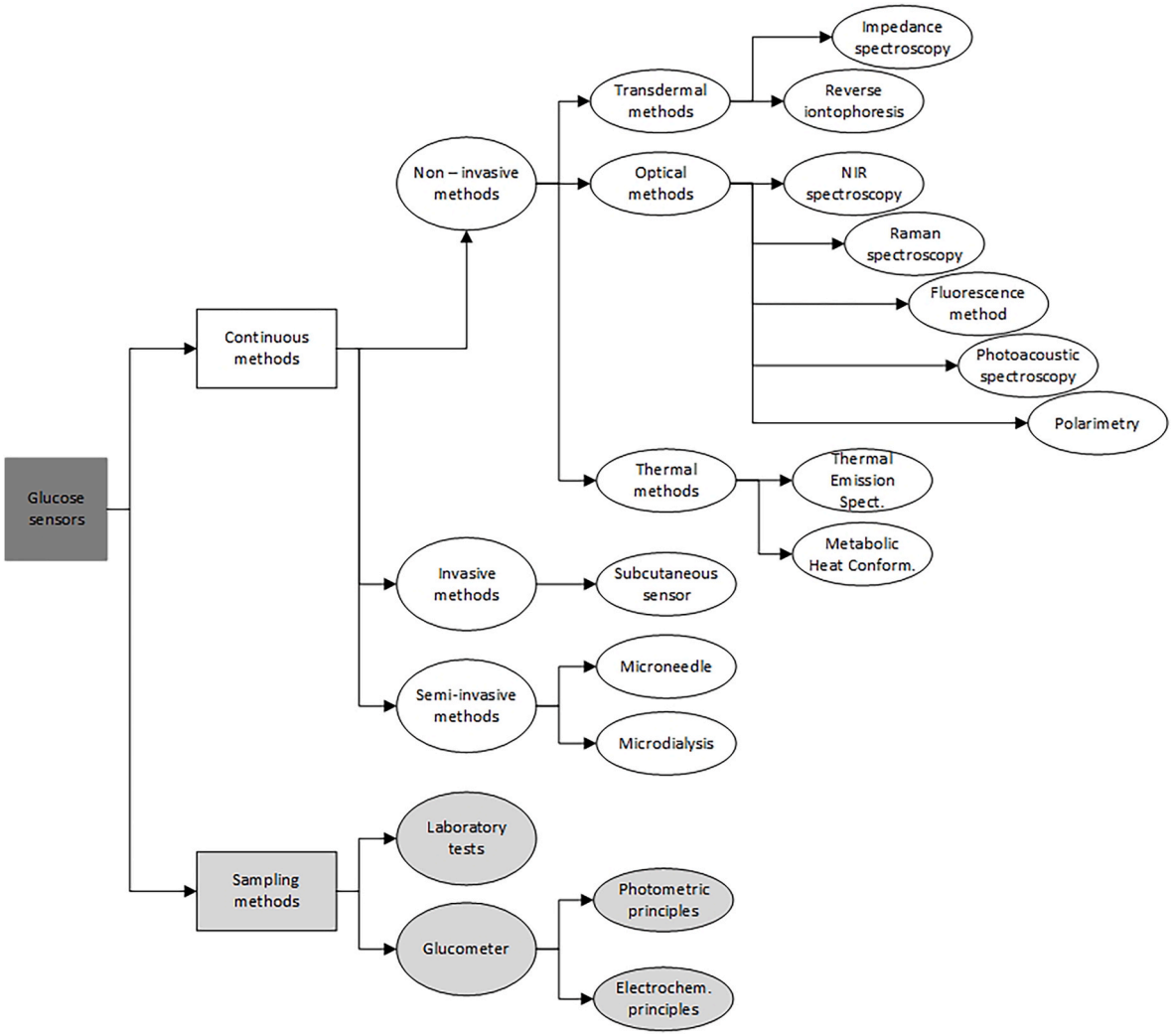


Fig. 4. Clear classification of glucose measurement methods.

addition to commercially available technologies, some methods are still under the research and development or under the test and validation phase. In Figure Fig. 4 an overview of techniques currently available or investigated is provided: as general criteria for the classification on the differentiation among a continuous and a discontinuous sensor is given on the top of hierarchy. These methods are further subdivided in terms of invasiveness. This is because this criterion drives the use the specific sensor and consequently the technology that is adopted for its realization. Some techniques are omitted following a critical assessment due to poor quality in terms of calibration and validation.

5.1. Continuous measurement

Continuous Glucose Measurement (CGM) is used for monitoring of glucose levels during the day. A diabetic person using a continuous monitoring system is able to respond immediately to any change in glucose concentration and prevent severe conditions. Mainly due to the simplicity of the method, the patient can monitor the blood glucose variations depending on the time, on the assumed food, on the physical activity or on the stress (Perdomo et al., 2000) (Yoo and Lee, 2010). Compared to others glucose measurements, the continuous method is much more convenient, because it allows to measure the glucose levels at regular time intervals, to store these values and to transfer the information to a personal computer. It therefore consists of three devices: a wireless receiver, a transmitter and a sensor. The transmission is provided by a wireless system embedded on the device, which provides to send data to a remote receiving unit. In order for communication to occur, the system must be paired, which works approximately 2 m (Lucisano et al., 2016). Continuous systems are designed for long-term monitoring of glucose concentration and these can maintain glucose sensitivity for several days (Joseph et al., 2015) (Levitt et al., 2017). Due to the comfort of the continuous method, the global market for these devices is estimated at approximately 788 million in 2020 (Kim et al., 2019).

There are several techniques for achieving a continuous measurement, such as relying on subcutaneous glucose measurement (interstitial fluid), blood or plasma glucose monitoring. However, interstitial fluid is most commonly used (Heller and Feldman, 2008) (Wallia et al., 2016) (Yoon et al., 2017). CGM systems use indirect sampling, by microdialysis or microperfusion, or measurement in adipose tissue. The needle type sensor is most often used. Enzymatic methods, fluorescence methods or analysis of the infrared spectrum are used. However, the continuous measurement of blood glucose concentration is affected by protein contamination of the electrode. Contamination causes a change in the sensitivity of the sensor and a possible risk of thrombosis. Therefore, techniques for measuring glucose concentration from an interstitial fluid can be a solution in this direction and have been developed also to overcome the described limits of blood monitoring. This technique is based on the assumption that the glucose concentration in the interstitial fluid is proportional to the blood glucose concentration and responds to changes in concentration without a major delay (Aussedat et al., 2000). Many studies have shown that the relationship between blood glucose and interstitial fluid glucose is not easy to be found. For example, the reaction that produces a change in blood glucose concentration after a meal is visible in the interstitial fluid after minimum 5–15 min, however, these times are not enough to capture rapid change. The length of the delay is also affected by the type of diabetes, the length of the disease and obesity (Chlup et al., 2015). In contrast, the change in insulin delivery is more readily visible in the interstitial fluid (Yoon et al., 2017). Therefore, calibration of the CGM system is necessary (Moser et al., 2016) (Wadwa et al., 2018).

In several studies, improvements in the stability of implantable glucose sensors have been studied: particularly remarkable is the possibility of fabricating sensors with nanofibres PANI and membrane E-PU (Fang et al., 2017).

As shown in Fig. 4, continuous methods are further subdivided in terms of measurement invasiveness, a description of the continuous methods used and available today is given and broken down in the following chapters.

CGM is often used in ICU's hospital ward, and randomized controlled trials have shown that insulin therapy and glycemic control in the ICU are challenging (Marik and Preiser, 2010) (Investigators, 2012) (Wernerman et al., 2014). The use of CGM in the ICU in combination with proper insulin therapy can improve positive outcomes in glycemic control and consequently increase the benefits for the patients (Wollersheim et al., 2016). In clinical environment continuous methods devices can be connected to central monitors and report blood glucose levels during the day, thus preventing hypoglycemia or other similar problems (Spanakis et al., 2018). However, it should be noted that in critical states, rapid changes in glucose concentration occur and today's existing systems do not have a fast-enough time constant.

5.1.1. Invasive continuous methods

Invasive continuous methods are based on obtaining an analyzed sample body fluid by breaking the patient's skin. Measurement invasiveness depends on the type of fluid being analyzed. Among the continuous measurement devices approved by Medical Authorities and available on the market it is possible to highlight the Dexcom system (Dexcom G4 Platinum Professional, Dexcom G5 Mobile, Dexcom G6 Pro), Medtronic system (Gurdian Link 3, Gurdian sensor 3, iPro2 Professional CGM, sensor Enlite) and the FreeStyle Libre system (Hwang et al., 2018) (Schaller et al., 2009).

5.1.1.1. Subcutaneous sensors. The most common procedure for the continuous measurement is based on an implantable "needle" type device that is inserted into the subcutaneous tissue, far enough to gain access to the interstitial fluid. It is a subcutaneous electrode and the most common area of application is the abdomen or arm (Aussedat et al., 2000) (Heller and Feldman, 2008). Its size in diameter is around 0.2–0.7 mm with a length of about 10 mm. Sensors must be inserted by the user into the subcutaneous tissues and replaced every 3 to 7 days (Lucisano et al., 2016). The length of the sensor implantation, ie its durability, is determined by the properties of the enzyme used, its immobilization and the protective membrane used. It is important to evaluate the possibility of local inflammation (Fang et al., 2017).

At least two electrodes are needed (working, reference), to ensure the stability of the potential, a larger area of the reference electrode is needed, for needle sensors this is ensured by the entire surface of the inserted needle. Here, a complication occurs in the arrangement of the system so that a large number of electrodes are not inserted into the body (Schmelzeisen-Redeker et al., 2013). The working electrode carries an immobilized enzyme and must provide a minimum polarization voltage to perform the reaction of about 600 mV, depending on the electrochemical active substances and materials. In the case of three electrodes, the demands on the reference electrode are not high, but at the same time it is a more complex and expensive system using a potentiostat. Another important component is the diffusion barrier preventing enzyme leaching and correcting the rate of glucose transfer to the electrode. At high transfer rates, the reaction with the enzyme may be saturated. The barrier also serves to correct oxygen, so it must be selectively permeable to oxygen, because it is necessary to ensure an excess of oxygen. It also minimizes the passage of interfering substances and prevents contamination (Cunningham and Stenken, 2009) (Nichols et al., 2013). It must not be forgotten that the whole system must be biocompatible to prevent or delay the inflammatory reaction or to prevent the formation of a dense collagen layer (Anderson and McNally, 2011) (Koschwanez et al., 2010) (Nichols et al., 2013).

The measurement of glucose is most often performed amperometrically using an electrochemical reaction using the enzyme GOx or other enzymes, which is immobilized on the electrode. Glucose oxidation is provided by oxygen or a redox mediator (Heller and Feldman, 2008).

Although the technique is indicated as a continuous measurement, in practical terms the measurement is based on sample analysis throughout a few minutes (Wernerman et al., 2014). Biosensors can measure every 10–20 s, but then the obtained signal is filtered so that the resulting time constant is most often 5–10 min with an average number of samples 50–150. Subcutaneous sensors are significantly affected by motile artifacts. The design of the puncture electrode is shown in figure Fig. 5. The first needle enzyme electrode was developed in 1982 by Shichitri et al. (Shichiri et al., 1982). The best possible immobilization of the enzyme with the mediator has been studied in order to increase the sensitivity of the sensor and thus longer shelf life (Kim et al., 2019).

In view of the above information, it is clear that the development is towards simple and reproducible manufacturability, which guarantees long enzyme stability and specificity, a sustainable diffusion barrier for glucose and oxygen transfer and, last but not least, a biocompatible membrane.

5.1.2. Semi-invasive continuous methods

Semi-invasive methods are based on the introduction of a hollow microneedle in places with a large number of capillaries and microdialysis is included here. These methods offer minimal measurement invasiveness.

1. Microneedle

The microneedle is used to obtain interstitial samples with minimal intervention and pain for the patient. They allow the rapid detection and analysis of body fluids and the acquisition of important physiological information, such as glucose levels. Glucose molecules diffuse into the cavity in the needle and are guided to the electrode. The device most often uses enzymatic amperometric measurement to measure glucose concentration (Wang et al., 2013) (Xue et al., 2018).

A big challenge and focus in this area is the use of the principle in wearable devices, the emphasis is on the miniaturization of devices (Joshi et al., 2020) (Yu et al., 2015).

2.Microdialization methods

The microdialysis is based on the flow of an isotonic buffer solution through the microporous fiber, and thus obtains the concentration of adipose tissue. There is a difference in glucose concentration between the flowing solution and the subcutaneous fluid, which depends on the flow and also on protein and cell contamination (Heller and Feldman, 2008). The main advantage of microdialysis is the fact that the sensor is outside the body and the properties of the perfusate can change the quality of the measurement. The sensor is then based on classical methods, most often using the GOx enzyme. Among all the features of a measurement apparatus, its friendliness of use is related also to the measurement accuracy (Heller and Feldman, 2008) (Yoo and Lee, 2010). Another possibility of continuous measurement is extracorporeal sensors in which the interstitial fluid is delivered to the sensor by microperfusion or iontophoresis method (Samant and Prausnitz, 2018) (Kolluru et al., 2019).

One of the manufacturers using microdialysis is Menarini Diagnostics, which introduced the GlucoMen® Day system consisting of a peristaltic pump driving the dialysis fluid into an established dialyzer. The sensor is then located outside the patient's body (Lucarelli et al., 2012).

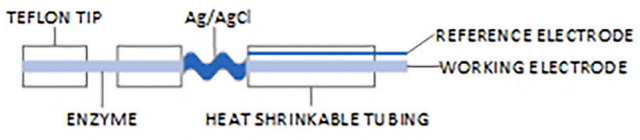


Fig. 5. The design of the puncture electrode.

5.1.3. Non-invasive continuous methods

Recent developments seek to exploit the characteristics of the glucose molecule at various frequencies in the spectrum, from DC and ultrasound to the near infrared (NIR) and visible regions. Non-invasive continuous methods are divided into two large groups, one using optical measurements and the other based on obtaining a sample on the skin of the body (Lin et al., 2017). It should be noted that the systems currently available do not achieve an accuracy comparable to traditional methods. In the literature and in the scientific research reports can be identified many non-invasive glucose measurement technologies, that are still in the early stages of development. Moreover, there are few and limited information on the safety and the efficiency of such kind of systems. In the available works describing these techniques, traditional methods and some non-invasive methods can be identified, together with available technologies used in practice (Corabian and Chojecki, 2017) (Eadie and Steele, 2017). For example, they presented a comprehensive search on non-invasive methods in the publication (Gusev et al., 2020) (Jain et al., 2021) (Kumar and Jayanthy, 2020) (Shokrekhodaei and Quinones, 2020).

Among the methods for non-invasive measurement of glucose levels, even if mostly they do not reach the level of accuracy of invasive methods, some of these can be taken in consideration for practical use reaching an acceptable level of performance (Uwadaira and Ikehata, 2018). As assessed, the main problem of these techniques is related to the difficulty to isolate the actual glucose level from other fluids. But at the same time, the great advantage in the possibility of the development of a non-invasive wearable device that is much more comfortable cannot be neglected (Rachim and Chung, 2019).

There are many devices for measuring glucose based on non-invasiveness. Some were able to obtain the necessary certificates and were commercially available, but with proven problems of accuracy or stability they were soon withdrawn from the market, others did not have sufficient funding. This group includes, for example GlucoWatch®, Pendra® či C8 Medisensors (Gandrud et al., 2004) (Potts et al., 2002) (Wentholt et al., 2005). At present, however, there are devices that are gradually being improved and are already on the market. Here it belongs Gluco-Track, Glucowise®, SugarBeat®, TensorTip Combo Glucometer (COG) (Gluco Track, 2021) (Gluco Wise, 2021) (Rojahn, 2014) (Segman, 2018) (DiabetesMine Team, 2019). An overview of individual technologies used in the devices is in Table 2.

6. Optical methods

Optical techniques are the most common methods for non-invasive measurement. These techniques do not use chemical reactions and therefore are not limited by the disadvantages related to the direct interaction with blood. The main advantage of optical biosensors relies in the resistance to biofouling from the absorption of proteins in the blood (Yoo and Lee, 2010). Thus, the physical properties of light in the analyzed interstitial fluid, in the anterior chamber of the eye, in tears, sweat or saliva are utilized. Other potential measuring points include fingers, lips, arms or earlobes (Delbeck et al., 2019) (Tronstad et al., 2019).

The most common applications of these biosensors are in non-invasive techniques that do not require access to blood vessels and in situ implants. Non-invasive sensors, however, are not accurate enough because are affected by interference that causes low signal strength and can have calibration problems due to the passage of multiple tissue layers (Kumar and Jayanthy, 2020). The wavelength of optical techniques is close to infrared radiation and the intensity of the detected light increases with higher blood glucose concentration, which is due to less dispersion. The most common optical methods are Near InfraRed detection (NIR) and Raman spectroscopy (García-Guzmán et al., 2017) (Ionescu and Doctorala, 2018) (Jernelv et al., 2019).

Table 2
Advantages and disadvantages of non-invasive method (Villena Gonzales et al., 2019).

Method	Advantages	Disadvantages	System
Near-Infrared Spectroscopy	• Low-cost materials • Sample preparation is not difficult, glass or plastic containers do not affect the measurement	• Measurements may affect the heterogeneous glucose distribution • Detection is not accurate for low glucose concentrations • Worse selectivity • High scattering level	• Combo Glucometer (Cnoga Digital Care, 2021) • NBM-200G (OrSense, 2021) • WizmiTM (Hadar et al., 2019)
Mid-Infrared Spectroscopy	• Low scattering • Good definition and specification of the absorption band • Better absorption than NIR • More accurate measurement of glucose concentration thanks to the MIR wavelength	• Small tissue penetration - reflection measurement only • Strong water absorption • High acquisition costs	–
Raman Spectroscopy	• Temperature changes do not affect measurements to a large extent • The measurement does not affect the water • High specificity	• Interference with other molecules (hemoglobin) • The wavelength and intensity of the laser are not stable • Long collection time • Sensitive to fluorescence or noise	• C8 Medisensor Glucose detector (Vashist, 2012)
Fluorescence	• Sensitive to very low glucose concentrations • High specificity • Concentration is measured from fluorescence intensity and decay time	• The measurement is sensitive to changes in pH and oxygen levels • Short lifespan of the fluorophore • There are limitations due to stability and poor recognition	• Eversense (2021) • Profusa (Profusa, 2021)
Photoacoustic Spectroscopy	• Simplicity • Not sensitive to water, NaCl, cholesterol, albumin	• Sensitive to temperature, movement noise	–
Reverse Iontophoresis	• Simple production and application • The correlation between blood and ISF values is good. • Use of enzymatic reaction	• Skin irritation may occur • Increases sweating • Does not detect rapid changes in glucose concentration	• GlucoWatch G2 Biographer (Kim et al., 2018) • SugarBeat (DiabetesMine Team, 2019)
Bioimpedance Spectroscopy	• Relatively cheap • Easy to use	• Sensitive to motion, sweat, variations of temperature, water • The measurement may be affected by physiological conditions	• Pendra (Medaval, 2021) • Biovotion (Biofourmis, 2021)
Thermal Emission Spectroscopy	• High selectivity for glucose • There is no risk of tissue damage	• Sensitivity depends on the thickness of the tissue • Interference by temperature fluctuations and movement	
Metabolic Heat Conformation	• Simple and well-known measurement of physiological parameters	• Large ambient noise • Measurement affected by sweat	• GlucoGenius (Carelife, 2021)
Radio-frequency (RF)/ microwave-millimeter sensing	• The signal penetrates deep into the tissues • No ionization side effects • Highly sensitive to changes in glucose concentration	• Glucose levels are affected by biological differences, physiological parameters	• glucoWISE® (Gluco Wise, 2021)

6.1. Near infrared absorption spectroscopy – NIR

Among the non-invasive methods the most used, based on optical technology, is the NIR. The system consists of a radiation source, diffraction grating, and a radiation detector. The NIR region is located in the region of 800–2500 nm. The vibrating bands of glucose are determined by the chemical composition of glucose (OH, CH, COH groups), and the main band lies at 1530–1850 nm in the NIR (Golic et al., 2003) (Tronstad et al., 2019). Since the energy of photons when applying the NIR technique is not high enough, it cannot cause electron excitation. In contrast, photon energy induces a change and cause vibrations. The vibration causes a change in the amplitude, a rotation of acceleration, and a change in the distance between atoms in the molecule. Each phenomenon causes some changes in the analyzed matter (Vahlsing et al., 2018) (Solihin et al., 2019). Three basic measurement modes are used: transmittance, reflectance and interactivity.

There is also the mid-infrared spectroscopy (MIR) method. It is used in the mid-infrared region, approximately between 2,5 μm - 25 μm (Khalil, 2004). MIR has a longer wavelength, so there is less scattering in the tissue, so the absorption rates are higher. The result is a very specific spectrum of glucose molecules in the MIR region. This spectrum is very well detected (Liakat et al., 2013). In addition to NIR and MIR, there is also a lesser nown method of infrated spectroscopy FIR 25 μm - 1 mm.

6.2. Raman spectroscopy

This method is based on the scattering of the monochromatic radiation, considering specific vibrating bands of the glucose molecular structure. The Raman spectra are usually sharper than classical spectra and do not have too many overlaps with other bands, thus avoiding accidental correlation with surrounding tissues. The photons of the radiation exchange energy with the succeeding photon present in the transmission medium, that has always a lower energy level than the previous one (Cote, 2001) (Scholtes-Timmerman et al., 2014). The difference between the wavelengths at the beginning and at the end of the vibrational state of the glucose molecule is evaluated, this difference is called the Raman shift (cm^{-1}). Vibration modes in the C — H (2900 cm^{-1}) and C — O, C — C (800, 1300 cm^{-1}) bands are used for glucose (Bumbrah and Sharma, 2016) (Villena Gonzales et al., 2019) (Wiercigroch et al., 2017).

Eye fluid can be used for Raman spectroscopy since water in the anterior chamber contains few Raman active molecules. However, it has to be considered that the blood glucose is approximately 20% higher than in eye fluid and changes in glucose concentration are detectable up to 30 min later (Kumar and Jayanthy, 2020) (Ergin et al., 2003).

6.3. Fluorescence method

Glucose concentration can also be measured using the fluorescence

phenomenon, since the presence of a glucose variation produces a chemical reaction with some specific monitoring substances introduced into the body. The technology is based on the principle of emitting fluorescent light at a specific wavelength after absorbing radiation of a different energy level, which causes a difference in wavelengths known as the Stokes shift. Fluorescent light is emitted with specific properties that are proportional to the glucose concentration. The source of this emitted light are fluorophores and intermediate molecules - receptors. Receptors are used because they bind more efficiently to glucose than fluorophores. Enzymes, boronic acid derivatives, specific proteins, and synthetic materials are used as receptors (L. Chen et al., 2018b) (Klonoff, 2012). The intensity or decay techniques measuring are used to analyze the fluorescent light produced. These products are scanned by optical methods and a CCD camera is often used (Hull et al., 2014) (Klonoff, 2012) (Pickup et al., 2013).

6.4. Photoacoustic spectroscopy

A possible method used for a non-invasive identification of the glucose level is the photoacoustic spectroscopy: this method uses a laser beam, with a wavelength range of 1000–1800 nm, to irradiate the skin. In contact with the skin, the radiation causes a temperature change, which causes volume expansion in an area illuminated by light and an associated photoacoustic wave is produced. This photoacoustic wave correlates with the concentration of glucose in the examined sample (Bolla and Priefer, 2020) (Gamessa et al., 2018) (Pai et al., 2017). There are also methods using ultrasonic waves propagating through an analyzed medium. There is a relationship between the concentration of glucose in the analyzed sample and the speed of propagation of the ultrasonic wave (Harman-Boehm et al., 2009).

6.5. Polarimetry

The basis of the method is the linear polarization of the well, where there is a change in the rotation of the vector clockwise due to chiral molecules, glucose belongs to this group of molecules and its concentration affects the size of rotation proportionally. Furthermore, different skin thickness or temperature contribute to the change in rotation. A laser beam from the region of ~ 780–400 nm is used. Since there is a large scattering of light when the tissue is polarized across the skin, the anterior chamber of the eye appears to be a suitable place for measurement. Thus, the reflected light is analyzed in terms of the angle of rotation and also the intensity (Malik and Coté, 2010) (Rawer et al., 2004).

7. Transdermal methods

Transdermal methods are based on obtaining interstitial fluid by a non-invasive method on the body surface, where the fluid is introduced into a glycaemic sensor. One of the best-known methods is reverse iontophoresis.

7.1. Reverse iontophoresis

Sometimes this method is classified as semi-invasive methods. In reverse iontophoresis, the glucose analysis is determined from the interstitial fluid or sweat using a galvanic current. The method is developed on the principle of electroosmosis and ion sodium movement in the presence of an electric field, considering that the human skin is physiologically negatively charged (Lipani et al., 2018) (Sieg et al., 2004). The device consists of two electrodes (anode and cathode), that are most often made of Ag/AgCl. Glucose is separated from the fluid and transferred to a hydrogel pad containing GOx, where the usual reaction takes place. It must be taken into account that the concentration of glucose thus obtained is lower than the concentration in the interstitial fluid measured subcutaneously (Heller and Feldman, 2008).

7.2. Bioimpedance Spectroscopy (BS)

Dielectric impedance spectroscopy is another method that is based on changes in glucose causing a change in permittivity and conductivity of the red blood cell membrane. In the field of measuring glucose concentration, a change in the concentration of glucose in the plasma is used with an effect on the concentration of sodium and potassium ions, the result changes in the conductivity of the red blood cell membrane. Alternating current is used, which is characterized by a known intensity and a small value (Tura et al., 2007) (Weinzimer, 2004).

8. Thermal method

Thermal methods use established physiological indices, which are derived from the formation of metabolic heat of the glucose molecule. These include Thermal Emission Spectroscopy and Metabolic Heat Conformation (Abd Salam et al., 2016).

8.1. Thermal Emission Spectroscopy

The basis of this method is in the generation of natural IR waves, the properties of the generated waves depend on the concentration of glucose in the alanyte. The energy emitted in the form of heat is in the range between 8 μm and 14 μm. A comparison with the calculated thermal energy using the Planck distribution function is used to correctly evaluate the glucose concentration (Buford et al., 2008) (Buchert, 2004). Fingers or earlobes are used for measurements. The method is considered to be relatively accurate and could be acceptable in the future for accurate non-invasive measurements.

8.2. Metabolic Heat Conformation

Metabolic Heat Conformation also deals with glucose concentration, this method is based on measuring physiological parameters, the fact is used that the oxidation of glucose generates heat as a by-product, the amount of heat correlated with the amount of glucose but also with the amount of oxygen in the body. The heat generated causes the surrounding skin to heat up. The proposed systems record the generation of heat, hemoglobin, oxyhemoglobin concentration, but also blood flow rate. The method uses spectroscopy and the sensor is located at the end of the finger (Tang et al., 2008) (Uwadaira and Ikehata, 2018).

9. Other non-invasive methods

In addition to these continuous methods, there are other methods by which glucose levels can be analyzed. However, these are methods that are often not validated, aren't used in clinical practice and their advantages and disadvantages are debatable. However, some of these methods need to be mentioned, as they are interesting research that can contribute to the improvement and friendliness of glucose measurement.

A significant group are methods using radio-frequency (RF)/microwave-millimeter sensing. The use of radio-frequency (RF)/microwave has the advantage of using less energy with less scattering in the tissue, which should cause it to pass deeper into the tissue, where it utilizes tissue characteristics such as reflection, absorption, etc. Analysis of these data examines the permittivity and conductivity of the tissue in relation to glucose concentration (Ebrahimi et al., 2020) (Hofmann et al., 2013) (Jang et al., 2021). Techniques based on the use of a microwave or millimeter radio system do not face interference and problems as with the use of optical methods, therefore these techniques are being further explored (Omer et al., 2020). This includes reflection techniques which, on the principle of reflection, especially the reflection parameter S11, analyze the amplitude and phase variation of the signal, changes in amplitude and phase are caused by a change in permittivity with a change in glucose concentration. Another possibility is the transmission technique, which is based on the calculation of the propagation of the

analyzed tissue based on the attenuation and phase insertion of the signal. The resonant perturbation technique can also be used, using changes in the resonant frequency, the so-called quality factor Q and bandwidth, which correlate with the properties of the test tissue, in particular the dielectric properties (Nakamura et al., 2016) (Kim et al., 2021). The implementation of a non-invasive glucose concentration monitor is also discussed in the publication (Choi et al., 2015), where they describe the first direct correlation measurements. The group also conducted a clinical study comparing device accuracy and repeatability (Choi et al., 2017). Based on the results, the group further deals with the solution of the device, but also focuses on understanding the physiological mechanism of the device in the context of the depth of penetration of microwave radiation and the capture of tissue permittivity (Choi et al., 2018).

Possible methods are, for example, Surface Plasmon Resonance, which works with electron oscillations generated at the dielectric-metal interface, analyzes the refractive index of the source monochmonatic light (Li et al., 2015). Another possible method may be Fluorescence using UV radiation to excite blood vessels and detect fluorescence at a given wavelength (Blodgett et al., 2011). Electromagnetic Sensing can also be used to measure glucose concentration, which records a change in the conductivity of the analyzed part in the context of a change in the glucose concentration in the sample (Melikyan et al., 2012). The possibility of measurement is also offered by the Ultrasound method, which with its principle is close to reverse iontophoresis (Lee et al., 2005) and Sonophoresis working with the permittivity of interstitial fluid that penetrates the skin surface (Rao and Nanda, 2009). Optical Coherence Tomography (OCT) is also one of the options that could be used in the future to analyze glucose concentration. Low coherent light is excited by the analyte, and an interferometric signal consisting of reflected and scattered light is monitored. The higher the refractive index, the higher the glucose concentration in the sample (Lan et al., 2017). There is also research based on the Time of Flight and THz Domain (Withayachumnankul and Naftaly, 2014). The migration of photons after a pulse of laser light is monitored.

There are also studies that analyze glucose levels from tears. The development of contact lenses for measuring the concentration of glucose from tears was discussed in publication (Lin et al., 2018). The authors used phenylboronic acid (PBA), which interacts with glucose, reversible changes in lens wall thickness occur. After the measurement, the image taken by the mobile phone is evaluated using the supplied software. Boric acid is used quite often to measure glucose concentration (Sivaev and Bregadze, 2018). There is also research working with a contact lens containing electronics to measure glucose concentration (Park et al., 2018). Glucose is analyzed from tears and the result is indicated by an LED. The contact lens contains miniature flexible electrical components (glucose sensor, wireless power transmission circuits, LED). In Study (C. Chen et al., 2018a), tears were also used to measure glucose levels. The measurement is based on the use of photonic crystal (PC) materials with monolayered colloidal crystals (MCCs), the whole concept is finally coated by 4 boronobenzaldehyde-functionalized poly (vinyl alcohol) hydrogels. Upon contact with tears, the system becomes discolored.

10. Advantages and disadvantages of non-invasive continuous methods

Table 2 shows the advantages and disadvantages of translated non-invasive methods. As already mentioned, these are largely methods that are in research and are not used clinically.

10.1. Application of continuous method with an insulin pump

These systems are called SAP systems (Sensor and Pump). The development of this technique has been extensive and demanding in terms of performance achievement, to guarantee good levels of accuracy and feasibility of insulin measurement and administration (Haidar et al., 2021) (Kowalski, 2009).

However, only open SAP system are fully utilized, and based on the information provided from sensors, a person is able to respond and deliver insulin. There are also closed systems, these systems are not fully functional today (Rashid et al., 2020), the sensor provides glucose reading levels, which are compared to a pre-set threshold; if the value deviates, an alarm triggers a control circuit and the pump automatically delivers insulin to the body. It can be also described as an alternative replacement of the pancreas functions (Albisser et al., 1974) (Shichiri et al., 1984) (Umpierrez and Klonoff, 2018). Systems are based on closed-loop regulator, where both dose estimation and personal bolus control are applied. The dual hormone systems (insulin, glucagon) represent another option (Rodbard, 2017) (Steil et al., 2006) (Adam et al., 2020).

However, it is important to highlight that the blood glucose level is dependent also on a large number of hormones and on the actual psychological distribution (Cocha et al., 2018). Another problem is the delay in the effect of the insulin delivered to the cell tissue compared to the release of insulin into the blood by the pancreas (Umpierrez and Klonoff, 2018). These problems affect and skew blood glucose measurements and may lead to a miscalculation of the amount of insulin administered. Many studies are investigating the safety of a hybrid closed system in patients with diabetes, as reported in (Bergenstal et al., 2016) and (Garg et al., 2017). Finally, as investigated in (Hemapriya et al., 2017) also a closed controllable loop system can be evaluated in terms of accuracy using an Error grid method.

Open systems include insulin pumps t:slim X2™, Animas Vibe and Roche Accu-Chek with glucose sensor Dexcom G6 and G5 or pump Paradigm Revel Pump with glucose sensor Enlite (Klonoff et al., 2017). Approximately 30–40% of patients with type 1 diabetes and an increasing number of patients with type 2 diabetes use this technology (Umpierrez and Klonoff, 2018). Fully enclosed systems that have received FDA approval in the US market are Medtronic MiniMed.

10.2. The future of continuous methods

Research in the field of continuous techniques aims at the development of a wearable system in combination with wireless communication with the parent central system and connection with an insulin pump in a fully closed circuit (Hemapriya et al., 2017) (Hosu et al., 2019). This development is aimed mainly at young and active people, but it is necessary to address the question and decision-making process for choosing the right system for different types of patients (Lodwig et al., 2014). One of the main problems preventing the full market penetration of the CGM system is the delay in changing the glucose concentration in the interstitial fluid relative to the blood glucose concentration and also the concentration dependence of the measurement accuracy, ie the lower the glucose concentration in the interstitial fluid, the less accurate the measurement. Thanks to fast research, however, the delay and accuracy of the measurement is compensated for, even thanks to the correctly set calibration (Yang and Deng, 2020). Another important parameter that enters the proper commercialization of the CGM system is its price. Insurance companies pay only part of the cost, and some patients find such CGM systems expensive (Yang and Deng, 2020).

Attempts to create a fully non-invasive system have so far been unsuccessful, and systems such as GlucoWatch or Pendra have been withdrawn from the market due to their low accuracy (Lin et al., 2017). A similar fate befell the contact lenses developed by Google and Novartis (Mandpe et al., 2020) (Tseng et al., 2018). Some of the techniques obtain the analyzed sample by an approach under the skin, there is an increased risk of infection, there is an opinion that after the creation of a fully non-invasive system, these methods should be abandoned. Nevertheless, research in this area is current and other alternative approaches are emerging. The representative is the K'Watch product of PKVitality from France (Wahid, 2020). Fluorescence research has been conducted by

systems such as Profusa or Eversense® from Senseonic in the USA, it should be added that both systems are in the development phase (Deiss et al., 2019). But even these efforts use partially invasiveness and so far face the problem of longevity.

A continuous painless approach is expected in the near future to provide equivalent overall performance compared to SMBG. The development of these techniques is closely linked to the promotion and introduction of new standards that would cover the required area. There is pressure to develop a quality and accurate non-invasive method of measuring blood glucose levels, which is still escalating in the context of patient friendliness. There are identified issues that are discussed and present research challenges. These include - continuous measurement without the current problem, accurate measurement of glycemia in connection with hypoglycemia and also affordable equipment. Most articles do not sufficiently discuss the problematic effects affecting the measurement, such as blood pressure, humidity, temperature or movement. These problems have been addressed, for example, in studies of wearable multisensor devices (Caduff et al., 2018) (Zanon et al., 2018). At present, there is also no system available that is able to compete in terms of acquisition costs and measurement accuracy. Most of the research available today focuses on the NIR and MIR methods, using the fact that the glucose molecule has specific absorption and vibration bands. Since these bands also overlap with the bands of other molecules and cause interference, the region of interest appears to be 1 MHz-1GHz; 100 GHz-30THz. The perspective is provided by a combination of different technologies that minimize measurement deficiencies and can compensate for errors. Artificial intelligence tools are coming to the fore, which can predict the development of glycemia and provide the necessary analysis (Contreras and Vehi, 2018) (Zarkogianni et al., 2015).

10.3. Invasive sampling methods

These methods are fully invasive and are based on obtaining a sample of the analyzed blood most often by injection. This includes both laboratory determinations, used to prove the disease and as a reference method, and a glucometer used for self-monitoring.

10.3.1. Laboratory determination

Most of the existing laboratory methods are used in the clinical environment to determine blood glucose levels and in general these are fully invasive. They are also a reference method for measuring blood glucose concentration with SMBG and CGM instruments. Reference methods used in the analysis of, for example, test strips include the use of ISY with the GOx enzyme or the hexokinase method. Both methods are combined with certified material that serves as a reference sample. The analysis of the glucose concentration in the reference sample is performed by reference measurement by mass spectrometry with isotope dilute gas chromatography. The manufacturer's recommended reference method should always be used to evaluate test strips, as differences in plasma glucose concentration analysis may differ by up to 8% between hexokinoxy and GOx methods. ISO 15197 describes the use of reference measurement. However, it is important to distinguish laboratory tests from reference measurements, even if the same methods are used, the reference measurement is linked to a reference standard (Andreis et al., 2014) (Chen et al., 2012).

In the case of laboratory techniques, this is a more time-consuming measurement, where several steps are applied. In most cases, these are larger instruments based on optical analysis of the sample (spectrophotometric tests). Belongs here enzymatic (GOx and peroxidase) and hexokinase methods. The enzymes glucose-6-phosphate dehydrogenase or glucose dehydrogenase may also be used. Methods are characterized by high accuracy, sensitivity, minimal cross-reactions and specificity. For SMBG and point of care, enzymatic methods are used more. The decisive factor here is the price, availability and simplicity of the method (Villena Gonzales et al., 2019).

Enzymatic methods are based on the use of the enzyme glucose oxidase GOx to oxidize glucose in the presence of oxygen and water and peroxidase. The reaction product is gluconic acid and hydrogen peroxide. Peroxidase serves to catalyze the reaction between hydrogen peroxide and the chromogen, thanks to which the chromogen is oxidized to an intermediate which couples to a soluble dye. Oxidative coupling is provided, for example, by a phenol derivative together with 4-aminoantipyrine to form a red color mixture. It is measured mostly by absorbance; the absorbance rate corresponds to the concentration of glucose in the sample.

$$glucose + O_2 + H_2O \xrightarrow{glucoseoxidase} gluconolactone + H_2O_2$$

$$H_2O_2 + colorless\ \ chromogen \xrightarrow{peroxidáza} 2H_2O + color\ \ product$$

The resulting product, in particular hydrogen peroxide, is further electrochemically oxidized, resulting in an amperometric signal that is proportional to the glucose concentration in the sample examination. The gas analyzers are often used to measure oxygen consumption and its rate in the oxidation of hydrogen peroxide, which corresponds to the glucose concentration (Villena Gonzales et al., 2019).

The hexokinase method uses the reaction of glucose with the enzyme hexokinase. The overall reaction results in the formation of reduced nicotinamide adenine dinucleotide phosphate (NADPH). The total amount of NADH coincides with the concentration of glucose in the analyzed sample. NADH has a specific property and can absorb light at 340 nm, spectrophotometry is used for this determination (Slein, 1965). The whole course of the reaction is given in Chapter 3.1.

Table 3 shows the most commonly used devices used in laboratory tests.

The test is performed from venous blood: from the whole blood, serum and plasma are extracted, and at present, only plasma glucose analysis is recommended (Chen et al., 2012). The venous blood is collected in a special tube designed to diagnose diabetes to prevent glycolysis and coagulation, containing an antiglycolytic agent (sodium fluoride, NaF/EDTA, NaF/oxalate, citrate buffer) and an anticoagulant (heparin). However, on the recommendation of the NACB (National Academy of Clinical Biochemistry) and the ADA (American Diabetes Association), the sample taken should be quickly placed in crushed ice and the plasma should be separated as quickly as possible (within 30 min). Plasma glucose is recommended, where the fasting physiological range should be between 3.3 and 5.6 mmol/l (Coward et al., 2019) (Sacks et al., 2011).

If the diagnosis is not unequivocally confirmed by the finding of venous blood plasma glucose (FPG) greater than 7 mmol/l, a glucose tolerance test (oGTT) is performed. If impaired glucose tolerance is found, OGTT is repeated at two-year intervals. The oral glucose tolerance test plays a key role in the diagnosis of gestational diabetes (Jagannathan et al., 2020).

The High-Performance Liquid Chromatography (HPLC) is a chromatology technique performed on liquids used to separate analyzed components from a sample to determine its concentration. It works with the liquid phase (mobile) and the stationary phase (immobile) of a substance that can assume both liquid and solid status (Dudchenko et al., 2016). The stationary phase is held in the form of a sorbent in the column through which the mobile phase driven by the pump flows. After the mobile phase has passed through the column, this phase is fed to a detector which records the physicochemical changes corresponding to the presence of the separated components. The result is recorded in the form of a chromatograph in which the separated components are indicated by a peak (Bornø et al., 2014). Thomas Schmid et al. used HLPC techniques along with UV detection: in a recent study they showed that carbohydrates can be detected in the direct mode at 266 nm using a UV absorbance detector by HPLC (Schmid et al., 2016). The same method was used by Esin Akgul Kalkan et al. (Akgul Kalkan et al., 2016 to perform a quantitative clinical diagnostic analysis of acetone in human blood. Another possibility offered by Zhaoli Ling et al. rely on the

Table 3
Device overview.

Enzymatic Method				
Equipment	**Type**	**Range**	**Sample**	**Sample volume**
YSI (YSI a xylem brand, 2021)	YSI 2900	5–2500 mg/dL	Blood, Plasma, Serum	10–50 μl
	YSI 2500	0–2500 mg/dL	Blood, Plasma, Serum	10–50 μl
Biosen (HaB Direct, 2021)	C-Line Clinic	9–900 mg/dL)	Blood, Plasma, Serum	20 μl
	C-Line GP+	9–900 mg/dL	Blood, Plasma, Serum	20 μl
	S-Line Lab+)	9–900 mg/dL	Plasma or serum	20 μl
Hexokinase method Equipment	**Type**	**Range**	**Sample**	**Sample volume** mg/dL
Beckman Coulter (Beckman Coulter Diagnostics, 2021)	DxC 800	3–600 mg/dL	Plasma, Serum, Urine, CSF	5 – 10 μl
	AU5800/ AU6800		Plasma, Serum, Urine, CSF	Ultra-small 1–25 μL
Abbott (Core Laboratory Abbott, 2021)	Architect c8000 Architect c4000	1–800 mg/dL	Blood, Plasma, Serum, Urine, CSF	1.5–35 μL Average: 7 μL
	Architect c16000	1–800 mg/dL	Plasma, Serum, Urine, CSF	1.5–35 μL Average: 7 μL
Roche Diagnostics (Roche Cobas, 2021)	Cobas c 701/702	2–750 mg/dL	Plasma, Serum, Urine, CSF	5.5 μL

possibility to combine HPLC with UV detection with PMP as a derivative for glucose quantification (Ling et al., 2016. Finally, another method recently developed is the refractometric detection of RI. The detection principle involves measuring the change in the refractive index of the effluent from the column passing through the flow cell (Ilaslan et al., 2015).

10.3.2. Glucometer

Glucometers are devices designed to perform regular blood glucose monitoring at home during the day. They are a tool for SMBG. The frequency of blood glucose analysis depends on many factors such as the type of disease (DM1, DM2), the diet and treatment prescribed, the insulin application and the general condition of the human body (Karapinar et al., 2020) (Seifert et al., 2016).

The basic element of this instrument is the test strips, where complete reaction and detection takes place. Glucometers use disposable detection strips that use photometric or electrochemical with amperometric detection. Both methods will be described in detailed in the following. Less common is the use of coulometric measurements for electrochemical strips (Kano et al., 2021). Modern glucometers most commonly used methods based on GOx, glucose dehydrogenase (GDH) or GD with pyrroloquinolinquinone coenzyme (PQQ-GDH) and on a smaller scale enzyme with nicotinamide (NAD-GDH) and flavinadenine dinucleotide (FAD-GDH) coenzyme (Galant et al., 2015). A clear comparison and description of the enzyme was given by Ferri et al. (2011). A comparison of individual enzymes is given in Table 4. Blood, obtained using a pen with an ejection needle (generally on a finger), is applied to the reagent strip or blood glucose test strip (Demitri and Zoubir, 2016) (CADTH, 2010) (Kosar et al., 2018) (Marius and Sever, 2019). The device itself is used to evaluate the analyzed sample, but also to store the measured values for subsequent analysis of the development of glucose values. Some glucometers allow you to enter time stamps before or after a meal, as well as to record various stimuli related to the development of blood glucose.

According to current recommendations, blood glucose control have to be executed a minimum of three times a day, also depending on the insulin regimen. For the measurement, 0.3–10 μl of blood sample is required and the appropriate range of glucose measurement is 1.1–33.3 mmol/l. The response speed is usually in the order of seconds (Galant et al., 2015). Blood is commonly obtained from the 3rd to 5th finger, but it is also possible to use alternative sampling areas such as the forearm, the abdomen or the thigh. It must be taken into account that, using alternative sampling sites, blood circulates differently and the blood glucose level measured may have different values (Palese et al., 2016) (Sagkal Midilli et al., 2019).

The decisive factor in choosing a glucometer to monitor glucose levels is to meet the quality requirements according to ISO 15197 (ISO 15197:2013, 2013). There is a large selection of glucometers on the market differing in principle, accuracy or used test strips (Klatman et al., 2019). A range of external factors (glucometer calibration, ambient temperature, blood drop size and quality, hematocrit, impurities, test strip age, etc.) may also affect the accuracy and the reliability of a

Table 4
Comparison and use of enzymes.

Enzyme	Cofactor	Properties
GOx (Yang et al., 2012)	flavin adenine dinucleotide	• High specificity for glucose • Low interference with galactose • The native electron acceptor is oxygen (it is not used in single-use strips, as it is not a robust method) - the need to use a mediator • Direct oxidation of the cofactor is not possible
PQQ-GDH (Wettstein et al., 2012)	pyrroloquinoline quinone	• Thanks to fast catalytic reaction - fast response • Interference with other sugars in native form (maltose, xylose, galactose) • Mutative form - high specificity for glucose with low activity with maltose • Oxygen activity does not occur • A number of mediators with suitable potential are employed • Direct oxidation of the cofactor is not possible
FAD-GDH (Lee et al., 2020)	flavin adenine dinucleotide	• Oxygen is not a native electron acceptor • There is no interference from changes in the oxygen partial pressure • FAD-GDH from bacteria - integrated electron acceptor (does not have such high specificity for glucose, activity with maltose) • FAD-GDH from fungi - the possibility of using a large number of mediators (high specificity for glucose, activity with 2-deoxy-D-glucose and xylose) • Direct oxidation of the cofactor is not possible
NAD-GDH (Kim et al., 2013)	nicotinamide adenine dinucleotide	• Good specificity for glucose • Because the cofactor is not bound to the enzyme, it is included in the immobilization process • Smaller amount of mediator due to the requirement for a fast response • Oxidation could occur directly on the electrode surface (theoretically - there is no return of NADH to its original form yet)

specific glucometer. The gold standard for assessing the accuracy of individual glucometers and the clinical severity of any errors are the Consensus Error Grids and MARD (Harada et al., 2019) (Krouwer and Garrett, 2019). The evaluation of the accuracy and efficiency of the meter based on the standard and error grids is discussed in more detail in Chapter 6.

The best-known manufacturers of glucometers include Abbott Diabetes Care, Roche Diagnostics, LifeScan, Arkray, Inc., Nova Biomedical, Ascensia Diabetes Care (formerly Bayer Healthcare). Since there are a number of glucometers, a comparison with the test strips is given in Table 5 in the following subchapter.

As with continuous systems, glucometers can be used in conjunction with an insulin pump. In this case, the insulin pump function is set using a data manager, which also contains a glucometer, and based on the measured values, data is sent to the insulin pump. Here you can use the Accu-Chek® Combo system (Roche Accu-Chek Combo, 2021). Another option is to use the CONTROUR PLUS LINK 2.4 m in conjunction with the MiniMed 640G insulin pump (Contour Diabetes Solution, 2021).

10.3.2.1. Photometric strips. Photometric strips are used to assess the blood glucose concentration directly on the test strip. With this technology, the reactants are stabilized in a dry layer at a specified location in the test strip. In addition to the enzyme, there is dye and the enzyme perosydase. These substances, when in contact with blood, react with glucose to form a colored compound (Demitri and Zoubir, 2016) (Wahl and Koschinsky, 2018). The resulting product is a chromogen often of dark red colour and the amount of this chromogen is given by the concentration of glucose in the analyzed blood. The colour intensity analysis is performed by saturating the chemical reaction between the reactants, and this slows the measurement time. The time evolution of the chemical reaction is divided into three points: 1) Degree of constant intensity (chemical reaction has not yet started), 2) Moisture time (blood is recognized by the reagent) and 3) Convergence (saturation phase of a chemical reaction) (Doi, 2019) (Seifert et al., 2016). Most often the intensity of the resulting colour is evaluated by photometers and spectrophotometers.

The photometric strips use the glucose oxidase reaction, where hydrogen peroxide can be used as the reaction product between glucose and enzyme, to oxidize the leuco dye under peroxidase catalysis and to determine the color product (red chromoform) photometrically, being the absorbance range between 505 and 520 nm (Galant et al., 2015) (Harada et al., 2019). A frequent application is the trinder oxidative coupling of 4-aminoantipyrine (p-aminophenazone, PAP) with an aromatic amine or phenol (usually substituted), e.g. 4-chloro-3-cresol. Other chromogenic acceptors may be: o-tolidine, indophenol or o-dianisidine (Galant et al., 2015) (Mohammadnejad et al., 2020) (Nakamura et al., 2008). They are also available dehydrogenase strips for glucose measurement. The reaction between glucose and the enzyme creates free electrons, which are transferred by mediators (quinonimine/phenylenediamine) to a redox indicator (phosphomolybdic acid). The redox indicator is characterized by a colour change at a certain electrode potential (Baygutalp et al., 2018) (D'costa et al., 1986) (Gilden, 2018).

The following figures Fig. 6 show the basic principles for measurement with the photometric principle.

The photometric principle was also used, for example, in publication (Ding et al., 2016) by means of the magnetic nanoparticles Greigite (Fe_3S_4 − MNP), which have peroxidase-like activity. Glucose is oxidized by the enzyme GOx to form H_2O_2. A colored product (blue) is formed from the enzyme substrate, it is catalytically oxidized with H_2O_2 in the presence of Fe_3S_4 − MNP. In general, this can be expressed by the following relationships:

$$S + E \leftrightarrow ES \rightarrow E^* + P_1$$

$$E^* + C \leftrightarrow E^*C \rightarrow E + P_2$$

$$P_2 + S + MNP \rightarrow (P_2SMNP)blue\ \ complex$$

Table 5
Overview of used glucometers.

Electrochemical principle					
Glucometer	**Measuring range** mmol/l	**Measurement time s**	**Sample materia a volume**	**Enzyme Strip**	**Enzyme**
Abbott Freestyle® Freedom Lite (Abbott Diabetes Care) **MyFreeStyle (2021)**	1.1–27.8	5	Capillary blood - 0.3 μL	FreeStyle Lite blood glucose test strips with ZipWik Tabs	FAD-GDH Mediator MAP
Abbott Freestyle® Optium Neo (Abbott Diabetes Care) **(MyFreeStyle, 2021)**	1,1–27,8	5	Capillary blood - 0.6 μL	FreeStyle Precision Neo (Optimum) test strips	NAD-GDH Mediator Phenanthroline quinone
Accu-Chek® Aviva Plus (Roche) **(Accu-Chek, 2021)**	1.11–33.3	5	Capillary blood - 0,6 μL	Accu-Chek Aviva Plus	PQQ-GDH (Mut-Q-GDH) Mediator Nitrosoaniline
OneTouch Ultra 2 (LifeScan) **(LifeScan, 2021)**	1.11–33.3	5	Capillary blood	OneTouch Ultra® test strips	GOx Mediator Hexacyanoferrate (III), Ferricyanide
Contour ™ Next USB (Ascensia Diabetes Care) **(Contour Next One, 2021)**	1.1–33.3	5	Capillary and venous whole blood - 0.6 μL	CONTOUR®NEXT Test Strips	FAD-GDH Mediator Phenothiazine
Glucocard Vital (Arkray, Inc) **ARKRAY USA (2021)**	1.1–33.3	7	Capillar blood - 0.5 μL	GLUCOCARD Vital Test Strips	GOx
iHealth GLUCO BG5 **(iHealth (2021)**	1.1–33.3	–	Capillar blood 0.7 μL	iHealth EGS-2003	GDH-FAD
MediTouch 2 (Medisana) **Medisana (2021)**	1.1–33.3	5	Capillar blood 0.6 μL	MediTouch 2 Test strips	GDH-FAD
Photometric principle					
Glucometer	**Measuring range** mmol/l	**Measurement time s**	**Sample materia a volume**	**Enzyme Strip**	**Enzyme**
Accutrend ® Plus system (Roche) **(Accu-Chek, 2021)**	1.1–33.3	12 s	Capillary blood - 15–50 μ L	Accutrend glucose	GOx
Accu-Chek Mobile (Roche) **(Accu-Chek, 2021)**	0.6–33.3	5	Capillary blood 0.3 - 5.0 μL	Without strip - replaced by test cartridges – Accu-Chek Mobile Test Cassette	Mut Q-GDH 2
Accu-Chek Active (Roche) **(Accu-Chek, 2021)**	0.6–33.3	5	Capillary blood - 1–2 μL	Accu-Check Active	Mut. Q-GDH 2

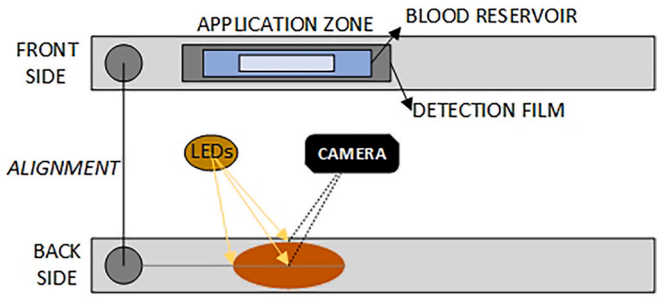


Fig. 6. The principle photometric strip.

10.3.2.2. Electrochemical strips. When using electrochemical strips, the analyzed blood is delivered to a measuring strip containing electrodes. After applying a blood sample in the form of a drop to a test strip, reactions between the immobilized enzyme and glucose take place to form a product, most often hydrogen peroxide. The product is further decomposed to produce a certain amount of current proportional to the glucose level. Besides the enzyme, that serves as a catalyst for the reaction, the test strip contains a mediator, that transfers electrons to the electrode. The reaction of the recruited cofactor of the enzyme with the oxidized form of the mediator thus creates a reduced mediator, which diffuses to the surface of the working electrode, at this point its oxidation takes place and the resulting signal is measured (Arango Gutierrez et al., 2018) (Guo and Ma, 2017) (Hatada et al., 2018).

The electrochemical test strip ensures an accuracy of 5–10% RMS error compared to laboratory tests, is quite fast, with an evaluation time in the range 5–15 s, and is patient-friendliness, needing 0.3 - 4.0 μl of blood (Heller and Feldman, 2008).

The construction of strips varies according to the manufacturer mostly in the number of electrodes used. The base of the strip consists of a plastic pad with electrodes, a small volume chamber and chemical components – a reagent formulation (stabilized enzyme, cofactors, oxidation-reducing mediator and surfactants), components of the mixture include, for example, polymers and buffers to maintain enzyme stability, pH, and an electrode system that detects a sufficient amount of sample for measurement. One of the most used methods of production of test strips is screen printing, where electrodes made of carbon or Ag/AgCl are also produced by this method. In some cases, the chemical components are mixed with carbon particles and applied together to a plastic strip. Electrodes made of other materials are made of thin layers and are applied to a plastic substrate, the shape of the electrodes is solved using a laser. The most common electrode layouts include the use of two or three electrodes system (Guo and Ma, 2017) (Paglinawan et al., 2018). The three-electrode system consists of a reference, working and supplying electrode. The working electrode must always have a precisely defined surface that is constant and is used for current sensing. The distance of the working electrode from the reading or reference electrode must be kept as small as possible to avoid a high electrolytic resistance between the electrodes. The reference electrode always keeps the voltage constant with respect to the working electrode to aid in the chemical reaction. The supply electrode is used to pass current between the working electrode. As no current flows through the reference electrode, a constant potential is ensured (Kuo et al., 2019). The structure of the convective enzyme test strip with a single reaction channel is shown in the following Fig. 7.

A dual channel test strip was studied and developed in (Guo and Ma, 2017): In this strip blood glucose is detected in channel 1 and uric acid (UA) is monitored in channel 2. The proposed strip is for patients suffering from diabetes and gout. The principle of two channel strips is shown in Fig. 8.

10.3.4. Overview of existing glucometers and test strips

A number of glucometers from various companies are available on the market. It should be borne in mind that the availability of meters is not the same in all countries and in the overview in Table 5 only discusses some representatives of meters from the most available manufacturers, which are based on both photometric and electrochemical principles. To complete the comparison, compatible test strips are listed for each meter, indicating the enzyme used.

Other representatives of Abbott Diabetes Care glucometers include, for example, FreeStyle Lite, FreeStyle Papillon Vision or FreeStyle Libre Pro (MyFreeStyle, 2021). The Roche Diagnostics family also includes Accu-Chek Aviva Expert, Accu-Chek Instant and Accu-Chek Performa (Accu-Chek, 2021). Lifescan also has a large selection of meters on the market, including OneTouch Verio Sync, OneTouch SelectPlus Flex or OneTouch UltraMini (LifeScan, 2021). Ascensia Diabetes Care glucometers include, for example, Contour Next or Contour Plus (Contour Next One, 2021) GLUCOCARD MX and GLUCOCARD X-meter glucometers are also manufactured, for example, by Arkray, Inc (ARKRAY USA, 2021).

10.3.5. Clinical significance of sampling method

As already mentioned, laboratory methods are used as reference gold standards for calibration and comparison of glucometers and continuous devices. In terms of measurement accuracy are unsurpassed, the disadvantage of laboratory techniques is the invasiveness of the measurement and longer time to achieve the measurement result.

The glucometer is the most reliable solution in the field of self-monitoring, it is a simple device using capillary blood with accurate acquisition of glucose. The glucometer is used several times a day and this is associated with a painful collection of blood from the finger. Another disadvantage of using a glucometer is the cost of test strips.

Both methods are the best solution for measuring blood glucose in terms of accuracy, on the other hand, these methods are associated with the inconvenience of measuring and thanks to the invasiveness of the measurement with contamination of samples. The invasiveness of measurements causes patients to avoid examinations, which is associated with a potential risk for late diagnosis.

10.3.6. The future of sampling and laboratory method

These techniques are at the peak nowadays, and there is little research into the development of new techniques. There is only an improvement of existing techniques in the form of immobilization, materials or scanning techniques for easier production, miniaturization and portability of equipment (Neves et al., 2017). Nevertheless, there are certain milestones that still need to be overcome (da Silva Neves et al., 2018). In the field of laboratory diagnostics, existing techniques are completely satisfactory, achieve high accuracy and sensitivity, and therefore there is no pressure on new methods.

As far as glucometers are concerned, photometric test strips are being withdrawn, replacing electrochemical test strips using mainly the GOx and DG enzymes. Although the functionality of the glucometer appears to be a solved innovation, it is shifting more in terms of connection with the superior system with software for management and processing of acquired data. Thus, the meters usually incorporate elements supporting Bluetooth connection, such meters are often referred to as smart meters

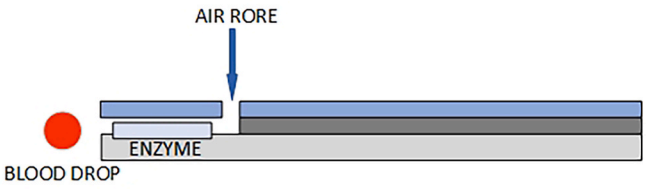


Fig. 7. The principle enzyme test strip.

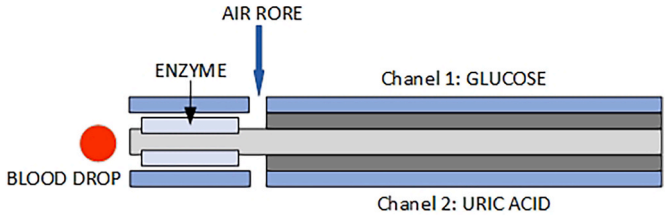


Fig. 8. The principe test strip with a dual reaction channel.

and have their own, mostly mobile, applications (Clements and Staggs, 2017) (Fu et al., 2017). Applications supporting better orientation in the data include, for example, Contour®Diabetes cooperating with the Contour®Plus One meter, data is automatically transferred from the meter to the application, the application serves to display the blood glucose trend but also as a classic diabetic diary, where sports activities, medications and take a menu. All stored information can be shared with the doctor (Contour Next One, 2021). Another application is VitaDock®, which supports the connection of multiple Medisana devices, such as smart scales, thermometers and the like. Blood glucose data is obtained from the MediTouch 2. The transmission is performed via Bluetooth or cable. Measured data and trend development can be visually displayed (VitaDock, 2021). The option is also offered by the iHealth Gluco SW with the connection of the iHealth BG5 meter (iHealth, 2021). One Touch Reveal® works with the OneTouch Verio Flex® Meter to feature ColorSureTM technology, which allows you to visualize the data you enter to make it easier to find a link between your blood glucose and your physical activity, diet and medication (OneTouch, 2021). The Accu-Chek Instant Meter is connected to the Accu-Chek® Connect Online application, in addition to the classic diabetic diary, it also supports an intuitive bolus advisor to help calculate the optimal insulin dose. There is also a platomorph that is supported on the Accu-Chek 360° PC (Accu-Chek, 2021).

10.4. Point of care analyzers

Point of Care's (POC) is a designation for point treatment by healthcare professionals (i.e. at the point of care testing - POCT). POCT is an integral part of laboratory diagnostics and the response time must be shorter than the laboratory response. An important factor for POCT is the Turn-Around Time (TAT). POC methods are separated from SBGM methods, they are characterized by higher demands on accuracy, hygiene or, for example, data collection requirements. A POCT analyzer can be in the form of a handheld device, a desktop analyzer or a disposable device. These analysers should be designed in a simple way for workers without specialized laboratory training (Akande, 2018). The diagnostic devices are based on the full venous blood, capillary blood or urine analysis. The most common POCT tests include tests for acid-base balance parameters, glucose, ions, drugs, viruses (HIV, hepatitis). The greatest advantages of POCT are its simplicity, the patient friendliness and its portability (Budianto et al., 2018) (Dincer et al., 2017) (Kiechle and Main, 2000) (Márquez et al., 2019).

There are analyzers that use disposable strips, but there are also analyzers that use multi-use cartridges. Analysis is performed using immunochemical methods, enzymatic analysis, or chemical reactions with an optically readable end of the reaction (Yoo and Lee, 2010). The resulting color is often evaluated, colorimeters are needed to quantify color intensity, but the current trend is increasingly using a lightweight integrated diagnostic reader. For the analysis of the glucose, electrochemical principles are mostly often used, where electrodes are printed on paper. The disadvantage of using the enzyme is in the durability of the strip (Nie et al., 2010) (Vashist et al., 2015). The most used devices include HemoCue® Glucose 201, Roche's Accu-Chek® Inform II and Nova Biomedical's StatStrip ™.

Consensus POCT12-A3 and POCT13, which provide the necessary guidance, have been established by the Clinical & Laboratory Standards Institute in order to review the POC system. The recommended guidelines have also been proposed by the FDA, the guidelines are close to the requirements of POCT12-A3 and POCT13, but they also focus on the system manufacturer himself (Nichols, 2020).

11. Requirements for glucose sensors and accuracy of methods

Glucose sensors are among the in vitro diagnostic devices or medical devices, they are part of the regulated market. In the United States, the Food Drug Administration - FDA is responsible for regulation, within the European Union, for example, Directives 90/385 or 93/42 EEC with conformity assessment by a notified body (Bhavyasri et al., 2019) (Food et al., 2012). If the device bears the CE mark, it can be sold in the EU (Bhavyasri et al., 2019). The differences between the American and European markets are not only in the area of regulation, but also in the classification of equipment. In the USA, glucose sensors for the treatment of DM, belonging to in vitro diagnostic devices, are classified as Class II devices and are approved by Annex 510 (k), where equivalence with a product already on the market must be demonstrated. Sensors belonging to medical devices are referred to as Class III devices and are part of the PMA (pre-sale approval) process (Santhosh and Kamaraj, 2018). Within Europe, in vitro diagnostic medical devices are certified according to 98/79/EC, this directive contains requirements for design, production or labeling before placing on the market, when proof of compliance with the directive is required (Bhavyasri et al., 2019). Invasive systems are assessed by Directive 93/42 EEC (The Medical Device Directive - MDD) (Pane et al., 2019), Class IIa includes easy-to-use systems. Systems that are used for more than 7 days are classified in Class IIb and biosafety and cytotoxicity tests are required (ISO 10993–1:2018, 2018). After proving conformity with the MDD, the product is marked with the CE mark. After the equipment is placed on the market, it is necessary to have a system of corrective and preventive measures in place. In order to obtain a permit to sell equipment, the company must implement a quality system according to 21 CFR 820 in the US or ISO 13485 within the EU (Bos, 2018) (Legum et al., 2019). Sensors are also subject to clinical trials approved by the Institutional Review Board (IRB) in the United States and approved by an ethics committee in the EU. CGM systems available today do not achieve the same precision as BGM systems. For CGM, for example, there are MARD-based Performance Metrics for Continuous Interstitial Glucose Monitoring POCT05 requirements that are close to ISO 15197 due to the comparison of reference values and CGM values (Freckmann et al., 2021). It should be noted that there are no specific standards for non-invasive glucose monitors. Manufacturers follow general guidelines developed for invasive methods to comply with national regulations (Villena Gonzales et al., 2019). Requirements proposals are already in the process.

Evaluating the accuracy and effectiveness of a blood glucose meter can be divided into two main parts: metric measurements to evaluate accuracy (mean-average-relative-measurement (MARD), the error grids) and guidelines for specifications, quality and other requirements arising from the standard ISO 15197, FDA (Danne et al., 2017).

11.1. Metric measurements

11.1.1. Mean Absolute Relative Difference—MARD

This is a very simple method of evaluating the accuracy of equipment for both SBGM and CGM. The basis is the calculation of the average of all absolute errors between the measured values and the reference values. The measured values of glucose concentration are obtained by the tested device and reference values are obtained by the classical laboratory method. The result is presented as a numerical value in percent. The disadvantage of this method lies in the impossibility of comparing two different tested devices, as the results depend on the details and settings of the performed testing (Reiterer et al., 2017).

11.1.2. Error grid

A frequently used method to determine glucose monitors is an error grid (Clarke error grid (CEG), consensus (Parkes) error grid (PEG), Surveillance error grid (SEG)) (Klonoff et al., 2014). CEG and PEG methods are older methods, the error grid evaluates the measured value of the sensor on the y-axis compared to the reference value of glucose on the x-axis and assigns a clinical risk to any glucose sensor error. The results fall into one of the five risk zones, designated for example A, B, C, D, and E. The areas are defined as follows: zone A - clinically accurate; zone B - benign; zone C - excessive; zone D - undetectable; zone E – faulty. After analyzing the distribution of a pair of paired points in the grid, the percentage of points in each zone is determined. An example of error grids is shown in Fig. 9 (Sutheran and Reynolds, 2016) (Tiberi et al., 2016). The newer SEG method uses a color scale to divide risk zones, which can detect both hypohlycemia and hyperglycemia (Wollersheim et al., 2016).

11.2. ISO 15197 and FDA requirements

The requirements of ISO 15197 apply to the all-available methods for blood glucose measuring. The FDA has proposed stricter requirements for instrument accuracy, and concerns have been raised about whether commercial systems can meet these requirements (ISO 15197:2013, 2013). Table 6 provides an overview of the requirements. The accuracy values given apply to testing at least three batches of 350 user test strips, with 10% of users being naive. Both ISO and FDA evaluations include real-user testing, as system accuracy results may differ from those tested by trained personnel. Numerous groups are involved in the evaluation of SMBG and POC systems (Freckmann et al., 2012) (Gijzen et al., 2012) (Klaff et al., 2015) (Link et al., 2015) (Sølvik et al., 2015).

Table 6
Overview of ISO and FDA requirements.

Relative number of results	ISO 15197		FDA	
	95 %		95 %	99 %
Within	±15 mg/dL	±15 %	±15 %	±20 %
At BG concentrations	<100 mg/dL	≥100 mg/dL	Entire range	
	99% of results within CEG zones A + B			

12. Discussion

The aim of the work was to create an overview of methods and ways to determine the glucose concentration in body fluids and outlining the further development of these technologies. The development of glucose control technology has made significant progress over the past decade in response to the demand of a growing global diabetic population. As diabetes mellitus is one of the most common diseases today and affects all age groups, it is clear that the economic impact is also increasing. Emphasis is placed on reducing the cost of treatment (Williams et al., 2020). Some of the existing methods are being used as a basis for glucose concentrations determining in clinically used medical devices and in vitro diagnostic devices. The given methods are, as the part of the search, primarily divided in terms of measurement continuity and further according to the invasiveness of the method, see Fig. 4. The above overview of methods and techniques for measuring blood glucose concentration shows that today's market offers a large number of possibilities and approaches to the issue. Laboratory methods, methods using a glucometer, or approved continuous methods have their place and application in the market. Individual methods cannot always be compared with each other, especially due to the focus and application of the methods. The principle of measuring blood glucose concentration is in most the cases based primarily on the electrochemical reaction between glucose and the enzyme, where glucose is most often obtained from blood or other body fluids. Enzymes, such as glucose oxidase, dehydrogenase are the most widely used today and the most accurate and widely used biosensors are based on their interaction with glucose. In this area, immobilization and detection techniques in particular are being improved. However, attempts have been made to create a non-enzymatic biosensor, but these researches are in their infancy and cannot currently be qualitatively evaluated (Promsuwan et al., 2019).

Discrete methods dominating in laboratory conditions are used as reference measures in clinical practice, and are most often based on enzymatic reactions, used for the diagnosis and periodic control of diabetes. Laboratory methods belong to purely invasive and discontinuous methods and use whole blood, especially separated plasma, to analyze the concentration of glucose in the blood. Glucometers are most often operated as orientation meters in domestic conditions due to easy affordability and the ease of operation. This method of measurement is sufficient to monitor the trend of blood glucose development and can capture significant changes in the trend of blood glucose development (Ottiger et al., 2016) (Seifert et al., 2016). The range of errors between the values obtained by the glucometer and the values obtained by the laboratory reference method is set to 15% (Andriankaja et al., 2019). The high repeatability and accuracy of these discrete measurements is mainly due to the analysis of whole blood. SMBG systems have been on the market for a long time and are constantly being improved, yet they are not as accurate as laboratory methods. There are studies that compare the obtained blood glucose level from venous blood using SMBG with the values from laboratory tests (Adnan, 2015) (Sato et al., 2019). The mean absolute difference is around 10.2–10.4 mg/dl with a MARD score of around 7%. Methods may be suitable for certain clinical applications where the measurement rate at the expense of glucose accuracy is acceptable. These include, for example, the POCT methods (Akande, 2018) (Márquez et al., 2019). Methods for long-term

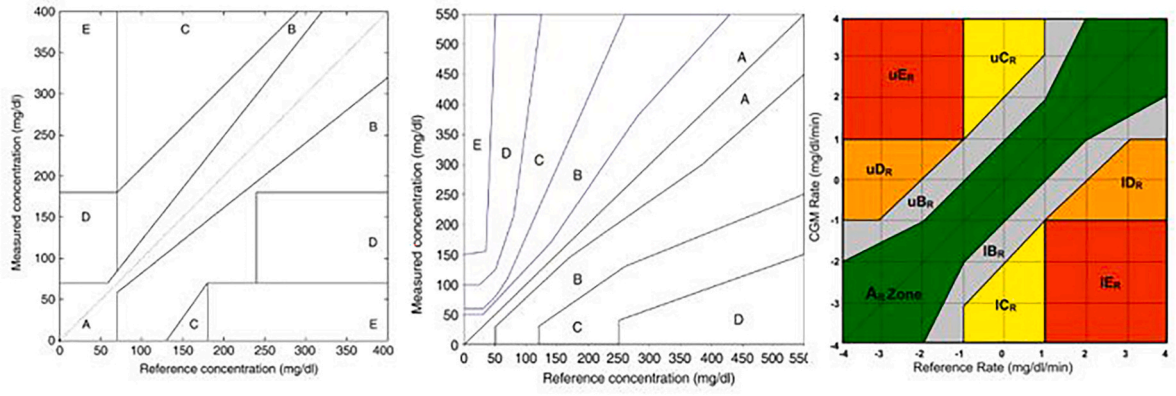


Fig. 9. Error grids: a) Clarke error grid; b) Consensus (Parkes) error grid; c) Surveillance error grid.

monitoring of trends in the body fluids glucose concentration, for example in telemetry applications, are also used in common practice (Holubová et al., 2018).

Opposite, continuous methods of glucose concentration measuring most often analyze the interstitial fluid, in which the development of blood glucose levels manifests itself with a time delay, which is typically up to 10–15 min. The magnitude of this delay is influenced by factors such as the physiological condition of the patient as well as the technical parameters of the sensor, the reaction time of the sensor in terms of diffusion, where pulse waves and data acquisition into digital form or signal processing time are expressed (Klonoff et al., 2017). The absolute values obtained using continuous invasive and semi-invasive methods do not correspond to the results of reference laboratory methods, but are linearly dependent (Aussedat et al., 2000) (Chlup et al., 2015). It is known from the research that continuous methods are used in conjunction with an insulin pump, where it serves as a control part (Cocha et al., 2018). This application is very important to replace the function of the pancreas. For this reason, many teams are focused on improving and, in particular, refining continuous methods so that they can respond to rapid changes in the body and provide accurate feedback for the insulin pump. Further research should therefore be focused both on the possibilities of detection the emerging signal approaching continuity and on improving immobilization techniques. Another area, that is found interesting, is the development of glucose prediction and their trends. Glucose prediction is mainly used in conjunction with an insulin pump and insulin control. Some research results have already been published in this area (Oviedo et al., 2017) (Pérez-Gandía et al., 2010) (Zecchin et al., 2015), where neural networks and their modifications are used, but there is a need to further developing the work. A big problem with continuous methods arises with its use, when patients seek simplicity and friendliness at the expense of accuracy and performance of CGM. It is futher clear that the design of the sensor today has to deal with several compromises. These mainly include accuracy vs comfort; comfort vs features. Painless and easy application is already a standard today and requires an intelligent design solution that can also solve the issue of production costs. Furthermore, it is necessary that the control of the entire system be simple, even the subsequent work with measured data (Bibbo et al., 2016). The accuracy and reliability of CGMs are identified as the biggest obstacle to recognizing the reliability of systems and are reflected in the perception of these systems by the user, where they are not yet perceived as a substitute for point measurements. Especially at values close to the hypoglycemic tent, the accuracy of the system is very important and CGM is a frequently discussed problem, because at these low values the measurement is still suboptimal (Clarke and Kovatchev, 2020). Although accuracy and reliability solutions are addressed by numerous groups, it is anticipated that CGM calibration will still be required. As a result, the proposed systems must use less calibration time, last longer, be comfortable, and integrate with the insulin pump (Acciaroli et al., 2020). The information obtained from revievs suggests that the adoption and use of new glucose detection technologies is inevitable and close to reality.

High pressure is being exerted on diabetics to develop a non-invasive continuous method that would ensure accurate measurements. Here, however, specific spectroscopic or other interfering properties of glucose still stand in the way, which have not yet been effectively overcome. Today's research relies mainly on optical and infrared methods, but the question arises as to whether, in the case of non-invasive methods, it will not be necessary to combine more technologies together to underline and minimize errors (Uwadaira and Ikehata, 2018). Optical and NIR methods face a big problem of interfering substances but also sensitivity to movement, on the other hand, methods using ultrasound, for example, do not have these problems, but they face others. Continuous non-invasive methods for measuring glucose concentration in body fluids are under the development (Hull et al., 2014) (Sieg et al., 2004) (Solihin et al., 2019), they are not currently validated for clinical practice with regard to their accuracy in both discrete and continuous mode, and the accuracy of these methods has not been published with regard to reference methods. Research teams try to detect blood glucose levels from, for example, interstitial fluid, sweat or tears, or using infrared or other radiation (Gamessa et al., 2018) (Lin et al., 2018). Methods based on determining the concentration of glucose from sweat or tears are used in wearable devices to promote a healthy lifestyle.

The survey clearly shows that the development is focused mainly on the improvement of continuous methods, which come to the foreground, and also on the development of a biosensor that would be purely non-invasive and continuous. Existing continuous methods do not measure the blood glucose level continuously, but even in this case it is a discrete reading of the glucose concentration, which is considered continuous by the manufacturer during sampling and analysis. However, the number of samples is within seconds, which is fully sufficient to monitor the development of blood glucose levels in diabetics from a clinical point of view, but for other experimental applications there may be a requirement for a truly continuous measurement of blood glucose concentration. The main problem with these techniques is measurement inaccuracy and usability issues, which is why most of the devices (Pendra, GlucoWatch) that have been placed on the market have been withdrawn from the market. A similar fate awaited contact lenses that analyzed glucose from tears (Senior, 2014). Although there is no accurate and proven continuous non-invasive device on thru yet, the path to it no longer seems so far-reaching. In recent years, great progress has been made not only in technology but also in regulation, which suggests that the production of such equipment is achievable. Availability of accurate and reliable equipment for rapid assessment of glucose concentration without skin puncture will revolutionize glucose monitoring at home and in the hospital.

As has been mentioned many times, biosensor technology has the most common application in the field of blood glucose measurement. There was great motivation to solve obstacles with measurement in the field of biochemistry, production and in improving measuring methods. The state of the art is the result of four decades of development, and progress has made it possible to measure different glucose concentrations in different interfering environments. Thanks to the improvement of production technology, the production of biosensors has expanded, especially in the area of test strips, thus reducing their price. The same trend is expected for the CGM sensor, where the performance problem must first be solved, yet even here we can talk about great progress in terms of accuracy and friendliness of measurements. It is expected for a CGM system. That it provides greater comfort, flexibility and allows a more equitable adaptation of the diabetes trap.

13. Conclusion

The presented review presents currently available and used methods for measuring the concentration of glucose in the blood and other body fluids and their technical description using. It also provides information on the development trend in the field of non-invasive continuous methods. The article also introduces the basic tools for evaluating their accuracy. The discussion discusses the technical development and development of future devices that can monitor glucose concentrations non-invasively. However, the level of measurement accuracy of these techniques is also discussed, as the detection of sharp fluctuations in concentration is very important in critical patients.

From the current state of research on the determination of glycaemia in body fluids, it was found, that in terms of accuracy, there is no comparable method of measurement with the invasive discrete laboratory method, which is a standard and is used as a reference method to determine glucose concentration.

Continuous non-invasive methods are currently being developed and pilot results can be expected in optical, transdermal and thermal methods. Existing methods based on continuous invasive measurements have a minimum reading time of individual formulas in the order of

minutes. Therefore, it is not a real-time measurement method indeed; it is a sequence of discrete samples due to the kinetics of ongoing electrochemical reactions to determine blood glucose levels. For many applications, this measurement interval is sufficient, but with technological progress, the need to shorten the measurement interval or the requirement for really continuous measurement of glucose concentration can be expected, for example to control insulin pumps.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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