Insight into continuous glucose monitoring: from medical basics to commercialized devices

Ayman Chmayssem, Malgorzata Nadolska, Emily Tubbs, Kamila Sadowska, Pankaj Vadgma, Isao Shitanda, Seiya Tsujimura, Youssef Lattach, Martin Peacock, Sophie Tingry, et al.

Insight into continuous glucose monitoring: from medical basics to commercialized devices

Ayman Chmayssem,[1] Małgorzata Nadolska,[2] Emily Tubbs,[3,4] Kamila Sadowska,[5] Pankaj Vadgma,[6] Isao Shitanda,[7,8] Seiya Tsujimura,[9,10] Youssef Lattach,[11] Martin Peacock,[12] Sophie Tingry,[13] Stéphane Marinesco,[14] Pascal Mailley,[15] Sandrine Lablanche,[4,16] Pierre Yves Benhamou [16] and Abdelkader Zebda[1,9*]

[1] Univ. Grenoble Alpes, CNRS, UMR 5525, VetAgro Sup, Grenoble INP, INSERM, TIMC, 38000 Grenoble, France
[2] Institute of Nanotechnology and Materials Engineering, Faculty of Applied Physics and Mathematics, Gdansk University of Technology, Gdansk, 80-233, Poland
[3] Univ. Grenoble Alpes, CEA, INSERM, IRIG, Biomics, F-38000, Grenoble, France
[4] Univ. Grenoble Alpes, LBFA and BEeSy, INSERM, U1055, F-38000, Grenoble, France
[5] Nalecz Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, Ks. Trojdena 4, 02-109 Warsaw, Poland
[6] School of Engineering and Materials Science, Queen Mary University of London, Mile End, London E1 4NS, UK
[7] Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba 278-8510, Japan
[8] Research Institute for Science and Technology, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba 278-8510, Japan
[9] Japanese-French lAaboratory for Semiconductor physics and Technology (J-F AST)–CNRS–Université Grenoble Alpes–Grenoble, INP–University of Tsukuba, 1-1-1 Tennodai, Tsukuba, 305-8573, Japan
[10] Division of Material Science, Faculty of Pure and Applied Science, University of Tsukuba, 1-1-1, Tennodai, Tsukuba, Ibaraki, 305-5358, Japan
[11] MADELECS, 77C, Avenue Jeanne d'Arc, 38100, Grenoble, France
[12] Zimmer and Peacock, Nedre vei 8, bldg 24, 3187 Horten, Norway
[13] Institut Européen des Membranes, IEM UMR 5635, Université Montpellier, ENSCM, CNRS, Montpellier, France
[14] Plate-forme technologique BELIV, Lyon Neuroscience Research Center, CNRS UMR5292, Inserm U1028, Univ. Claude-Bernard-Lyon I, 69675 Lyon 08, France
[15] Univ. Grenoble Alpes, CEA, LETI, DTBS, F-38000 Grenoble, France
[16] Department of Endocrinology, Pôle DigiDune, Grenoble University Hospital, Univ. Grenoble Alpes, Grenoble, France

* Corresponding authors:
abdelkader.zebda@univ-grenoble-alpes.fr
ayman.chmayssem@univ-grenoble-alpes.fr

Abstract

According to the latest statistics, more than 537 million people around the world struggle with diabetes and its adverse consequences. As well as acute risks of hypo- or hyper- glycemia, long-term vascular complications may occur, including coronary heart disease or stroke, as well as diabetic nephropathy leading to end-stage disease, neuropathy or retinopathy. Therefore, there is an urgent need to improve diabetes management to reduce the risk of complications but also to improve patient's quality life. The impact of continuous glucose monitoring (CGM) is well recognized, in this regard. The current review aims at introducing the basic principles of glucose sensing, including electrochemical and optical detection, summarizing CGM technology, its requirements, advantages and disadvantages. The role of CGM systems in the clinical diagnostics/personal testing, difficulties in their utilization and recommendations are also discussed. In the end, challenges and prospects in future CGM systems are discussed and non-invasive, wearable glucose biosensors are introduced. Though the scope of this review is CGMs and provides information about medical issues and analytical principles, consideration of broader use will be critical in future if the right systems are to be selected for effective diabetes management.

Keywords

Diabetes, continuous glucose monitoring, biosensor, artificial intelligence.

List of abbreviations

AI- Artificial intelligence
BG- blood glucose or glycemia
CGM- continuous glucose monitoring
DM- diabetes mellitus
Fox- forkhead protein family
GDH- Glucose Dehydrogenase
GOx- Glucose oxidase
GV- Glycemic variability
HbA1c - Glycated hemoglobin or glycohemoglobin
HNF- hepatic nuclear factor
ISF- interstitial fluid
LoD- limit of detection
MARD- Mean absolute relative difference
NIDDM- Non-insulin dependent diabetes mellitus
PB- Prussian blue
POC- point-of-care
RF- radio frequency
RP- Ruthenium Purple
SMBG- self-monitoring of blood glucose
SREBP- sterol regulatory element-binding protein
T1D- type 1 diabetes
T2D- type 2 diabetes
WBSs- Wearable biosensors

1. Introduction

Diabetes mellitus, commonly referred to as diabetes, is a wide spectrum disease affecting both children and adults and requiring complex and long-term treatment. According to the latest statistics from the International Diabetes Federation, 537 million of adults are currently living with diabetes and this number is expected to increase to 643 million by 2030 [1]. Currently, 1.5 million children and adolescents under the age of 20 suffer from type 1 diabetes (T1D) [2]. T1D is an autoimmune disease that causes damage to the insulin-producing cells, known as beta-cells, part of pancreatic islets cells [3, 4]. Patients with T1D must therefore monitor their BG levels or glycemia several times a day in order to adjust their insulin (hypoglycemic hormone) levels by sub-cutaneous injections, currently the only therapeutic strategy. Maintaining BG level is essential to avoid complications such as chronic coronary heart disease, diabetic retinopathy, nephropathy and neuropathy related to elevated glycemia. There is also a high risk of life-threatening metabolic crisis and dangerous central nervous consequences with low glycemia that can lead to coma [5]. It is noteworthy that the cost and access to treating long-term complications accounts for more than 30% of diabetes management costs [6–8]. According to the American diabetes association, in 2017, in the USA alone, this cost was estimated around 100 billion USD [9]. Finding a way to maintain normal blood glucose levels in every patient is therefore of crucial importance, from both a healthcare and economic point of view.

Current methods of self-monitoring of blood glucose include point-of-care (POC) systems using electrochemical devices with enzymatic electrodes, manufactured as printed strips, and are capable of quantifying blood glucose in microliter drops of whole blood [10]. These devices have been a dominant part of commercial point-of-care devices allowing patients to monitor their own glycemia levels. However, these devices require repeated pricking by the patient several times a day to maintain adequate blood glucose levels and limit complications [11, 12]. Although if POC devices are now accurate enough to allow reliable personal BG monitoring, they do not allow continuous control and it is not possible to

integrate feedback control of this type of self-monitoring of glycemia [13]. POC devices do not allow glucose monitoring during sleep, which allows for episodes of elevated or decreased glucose at night, thereby limiting the extent of glucose control in the patient's life. Moreover, such devices have a high impact on patient quality of life and may be a barrier for some patients in their practice of efficient glycemia controls. In particular, because diabetes is a chronic disease, many years of pricking fingertips can lead to loss of sensitivity and discomfort [14, 15].

Among studies in the field of improved monitoring, interstitial glucose monitoring systems (intermittent or continuous) have shown the most promise [16]. If they are not all yet commercialized, their ability to easily monitor glucose levels throughout the day and night allows a more efficient control of glucose level, with significant benefits for patient quality of life and quality of glycemic control [17–20]. These are generally minimally invasive devices in which sensor electrode is inserted subcutaneously and used to measure glucose concentration in the interstitial fluid (ISF). The one-step insertion under the skin with a needle can be performed independently by the patient [21]. In order to reflect the real glucose value in blood, it is necessary to carefully choose the location of the sensor in contact with the interstitial fluid. The chosen environment must be well vascularized, as glucose must diffuse from blood vessels into the interstitial space where the sensor surface is located. Common locations include the upper arm, chest, hip or thigh. Good vascularization is usually the case for most devices acutely implanted, but can become a problem when fibrous tissue accumulates around the sensor [22]. However, regardless the location chosen for the insertion of the sensor, it should be taken into account that there is a delay for equilibrium between blood and tissue glucose levels, estimated around 5 to 30 minutes, partly due to diffusion time [23].

This review discusses the basics of diabetes from a physiological and cellular perspective. It explains how deregulation of blood sugar levels leads to diabetes problems. The therapies for diabetes available today are presented. The second part of this review discusses the tools for glucose monitoring in diabetes, and describes in detail the principles of glucose biosensing from a technical point of view. The different CGM systems (invasive and implantable) available on the market are presented as well as the latest trends in non-invasive CGM systems. The last part of this review is dedicated to the trends of artificial intelligence in biosensing technologies and the future perspectives of glucose monitoring systems.

2. Diabetes basics

2.1. Physiological and cellular regulation of blood glucose level

Glucose is the predominant energy source in the human body and is consumed by all tissues, including the brain and muscles. It enters the bloodstream through intestinal absorption, glycogen breakdown (glycogenolysis) and gluconeogenesis [24, 25]. Glucose source for 70 kg person should be between 161 g to 270 g per day, depending on factors such as age, sex and activity level [26].
The concentration of glucose in plasma is about 5.5 mM in normal individuals. This value is tightly controlled by the balance between glucose absorption by the intestine, production by the liver, and absorption and metabolism by peripheral tissues [27]. In times of starvation, the depletion of circulating glucose and fatty acid stores causes the body to produce a hyperglycemic hormone, glucagon, by the cells of the pancreas in order to raise blood glucose levels. The insulin (hypoglycemic hormone) / glucagon ratio becomes low. The liver then produces glucose for glucose-dependent organs such as the brain, kidneys and red blood cells. The maintenance of blood glucose levels is therefore ensured by glycogenolysis and/or gluconeogenesis in the liver. Glucose can also be produced in the liver by oxidation of free fatty acids from lipolysis of adipose tissue to ketone bodies as metabolic fuel. During feeding, pancreatic cells secrete insulin, which stimulates the storage of glucose in the liver by synthetizing glycogen or fat via gluconeogenesis or lipogenesis respectively. In addition, insulin inhibits hepatic glucose production by inhibiting gluconeogenesis [28, 29]. Although the liver uses some glucose to meet its own energy needs, most of it is converted to glycogen. Excess of glucose is metabolized into acetyl CoA, which is used to form fatty acids, cholesterol and bile salts. Another means of processing glucose is the phosphogluconate pathway also called pentose phosphate cycle which provides NADPH

for these reductive biosyntheses [30]. Fatty acids from food are transported to the liver by chylomicrons where they will also be stored as triglycerides (Figure 1).

Insulin is secreted by the islets of Langerhans in response to increased circulating levels of glucose and amino acids after a meal. Indeed, in response to high blood glucose, pancreatic islets increase glycolysis and oxidative phosphorylation, creating ATP. The resulting increase in ATP concentration leads to Ca^{2+} signals that trigger exocytosis of secretory vesicles containing insulin [31, 32]. Briefly, the increased ATP:ADP ratio causes the ATP-gated potassium channels in the cellular membrane to close up, preventing potassium ions from being shunted across the cell membrane. The ensuing rise in positive charge inside the cell, due to the increased concentration of potassium ions, leads to depolarization of the cell. The net effect is the activation of voltage-gated Ca^{2+} channels, which transport Ca^{2+} ions into the cell. The rapid increase in intracellular Ca^{2+} concentrations trigger the export of the insulin-storing granules by a process known as exocytosis [33–35]. The ultimate result is the export of insulin and diffusion into the nearby blood vessels. Then, thanks to insulin receptors, insulin is targeted to peripheral tissues, mainly liver, skeletal muscle and adipose tissue, where it regulates metabolism. Indeed, insulin is the primary anabolic hormone promoting the synthesis and storage of carbohydrates, lipids and proteins, while inhibiting their degradation and release into the circulation. The insulin receptor is at the cell surface of its target tissues. Insulin binds to its receptor which results in the receptor autophosphorylation on tyrosine and then to the phosphorylation of intracellular proteins of the insulin signaling cascade leading to both mitogenic and metabolic effects of insulin [36, 37].
On the one hand, insulin stimulates glucose uptake in muscle and fat, and on the other hand inhibits hepatic glucose production. Therefore, insulin is the primary regulator of blood glucose concentration. Insulin has stimulating effects, such as the stimulation of cell growth and differentiation, but also promoting the storage of substrates in fat, liver and muscle by stimulating lipogenesis, glycogen synthesis. However, insulin also has inhibitory effects of lipolysis, glycogenolysis and protein break down [38].
In the liver, insulin stimulates the utilization and storage of glucose as lipid and glycogen, while repressing glucose synthesis and release. This is accomplished through a coordinated regulation of enzyme synthesis and activity. Insulin stimulates the expression of genes encoding glycolytic and fatty acid synthetic enzymes, while inhibiting the expression of those encoding gluconeogenic enzymes. These effects are mediated by a series of transcription factors and co-factors, including sterol regulatory element-binding protein (SREBP)-1 (in the ER) [39], hepatic nuclear factor (HNF)-4 [40], the forkhead protein family (Fox) [41] and PPAR co-activator 1 (PGC1) [42]. The hormone also regulates the activities of some enzymes, such as glycogen synthase and citrate lyase, through changes in phosphorylation state.

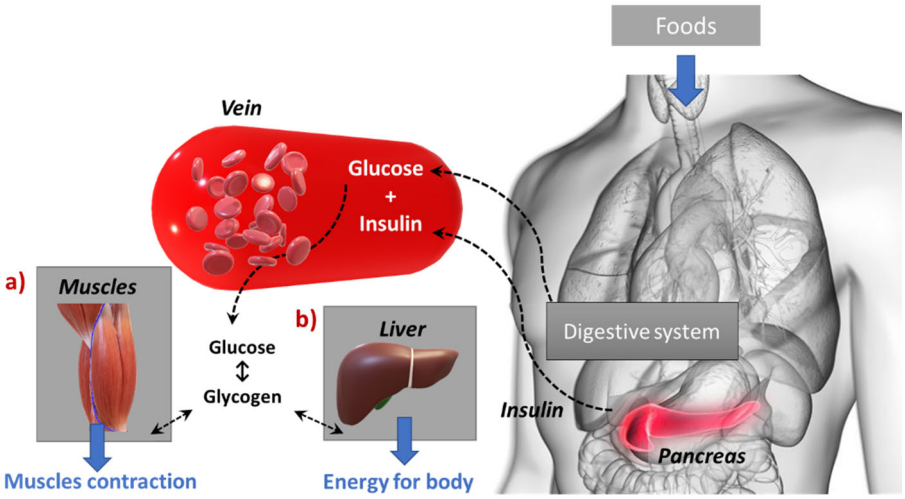

Figure 1. Simplified scheme of glucose cycle in the human body.

2.2. Diabetes: a deregulation of blood glucose levels

As mentioned in the introduction, unregulated blood sugar levels lead to many problems in the human body due to excess glucose in the blood, which does not contribute to the energy demand of the cells because of the non-permeability of the cell membrane. The disease is caused by a series of interactive features, due on the one hand to the sheer loss of the insulin secretory reserve, and on the other hand to a resistance of peripheral tissues to the action of insulin. There is no direct capacity to sequester glucose in the body, and therefore, coupled with hyperglycemia, there are high rates of glucose loss through urine. This glycosuria (the presence of glucose in urine) leads to dehydration and polyuria (excessive urine volume) [43]. Diabetes can thus have dramatic kidney mediated consequences, especially on body fluids and electrolytes. There are two main types of diabetes i.e., type 1 and type 2. Figure 2 explains how poor pancreatic insulin secretion can lead to type 1 diabetes (T1D) or type 2 diabetes (T2D). Type 1 diabetes is thought to be the result of an autoimmune process, the mechanism for which there is limited understanding currently [44]. There is a degree of genetic predisposition, but about 90% of people with T1D have no family history. Environmental factors are the most likely origin, somehow causative in triggering an autoimmune cascade. There is a high prevalence of T1D in people who have had a viral disease, such as rubella, conducting to a cytopathic effect that a virus may have on the body [45, 46]. In other words, the body's cells can deteriorate if a virus multiplies within them. If this multiplication effect directly affects the β-cells producing insulin, it causes type I diabetes. Regardless of mechanism, there is damage and progressive loss of insulin-producing β-cell mass with evidence of inflammation and infiltration by lymphocytes [47]. T1D involves the absence of β cells due to immune system destruction, and as there is no other source of insulin in the body, the inevitable outcome is escalating hyperglycemia. Currently, the only treatment strategy is insulin injection. Type 2 diabetes is not due to the production of non-functional insulin. Insulin produced is functional but the peripheric organ exhibit insulin resistant impairing insulin to act as expected. T2D can affect all ages, although it is most prevalent between the ages of 40 and 50. It has a slower onset, and may not be diagnosed as readily as Type 1 diabetes due to its environmental factors. It is associated with obesity, low levels of physical activity, particular eating habits and a generally sedentary lifestyle. However, it has a strong inherited component and certain ethnic groups also have increased susceptibility. This type of diabetes represents 90–95% of total diabetes mellitus cases (DM), also known as Non-Insulin Dependent Diabetes Mellitus (NIDDM), which is exemplified by resistance of the tissue toward the action of insulin or relative decrease in insulin secretion. Studies shows that the highest risk factor is weight: 80% of people with type 2 diabetes are overweight [48–50].

For the majority of healthy people, normal blood glucose levels are 4.0 to 5.4 mmol/L (72 to 99 mg/dL) fasting and up to 7.8 mmol/L (140 mg/dL) 2 hours after eating. For people with diabetes, blood glucose levels are 4 to 7 mmol/L before meals, and after meals up to 9 mmol/L for type 1 diabetics and up to 8.5 mmol/L for type 2 diabetics [51, 52].

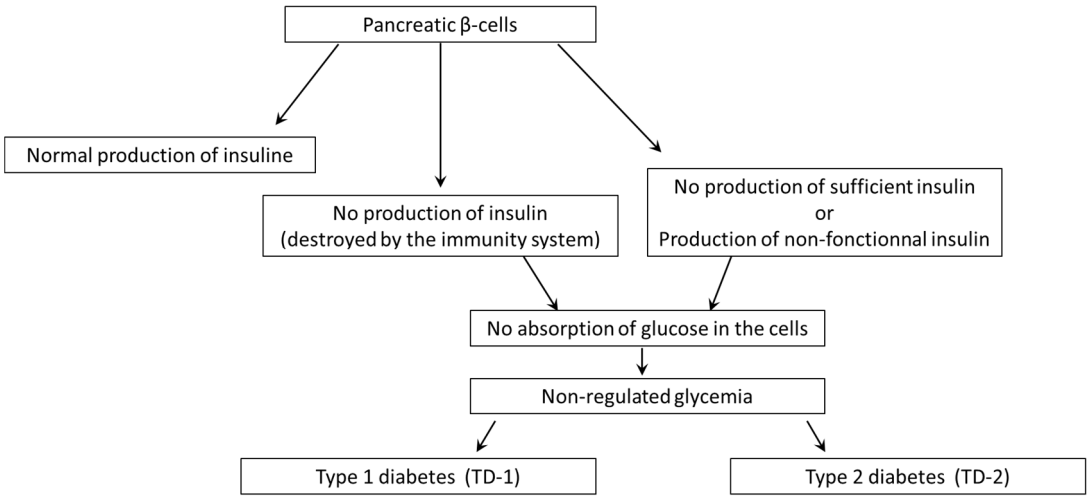

Figure 2. Type 1 and 2 cellular origin of diabetes.

2.3. Diabetes therapies: monitoring blood glucose level

People with T1DM are insulin dependent. For people with T2DM, the therapy is more open. Three modes of therapy can be distinguished: non-drug therapy, drug therapy and insulin therapy [53–55]. Non-drug therapy includes diet with a reduction in caloric intake and a change in the distribution of food intake, as well as an increase in activity. Drug therapy includes all drugs that help to regulate metabolic processes, and there is now a growing range of drugs that use a variety of pharmacological principles. The most widely used method of treating type 2 diabetes is insulin-therapy, which normalizes blood sugar levels in most patients. Insulin treatment requires several daily injections and self-monitoring of blood glucose levels, preventing long-term micro and macroangiopathic vascular complications and avoiding acute metabolic complications. Thus, diabetic complications can be delayed, or even prevented, by careful blood glucose management.

3. Tools for blood glucose monitoring in diabetics

3.1. Measuring blood glucose levels

Glucose monitoring is a pillar of treatment for patients living with type 1 diabetes and patient with type 2 diabetes treated by insulin. GM allow patients to adjust insulin dosage in order to control glucose levels. If glucose monitoring is fundamental to achieve glycemic control, its practice has long been based on capillary blood glucose control [56, 57]. This technique was limited by the patient's ability to perform no more than 4 to 10 blood glucose checks per day without impacting quality of life. With capillary glucose monitoring, the ability to monitor glucose during the night is particularly challenging.

Point-of-care devices based on interstitial glucose monitoring system (intermittent or continuous) are therefore a major advance over capillary glucose control [58, 59]; the description and operation of these devices will be discussed in the second part of this review.

3.2. Glycemia detection sites

The history of glucose testing began in the early 20th century and was first based on monitoring of glucose in urine samples [60]. First tests were based on colorimetric tests, for more than 50 years. Since then, urine glucose tests were further developed and even today they act as fast and easy screening method in medicine. However, the main limitations of such tests are that urine glucose do not reflect the level of BG and glucose is usually not detectable in the urine until the levels are high enough [61–63]. Thus, many other body fluids have been also proposed as BG detection sites, which can offer more sensitive and real-time monitoring. Figure 3 summarizes potential glucose measurement sites with the mean expected value for normal fasting blood glucose concentration.

3.2.1. Blood

Glucose monitoring (GM) directly in blood samples began in the 1960s with the use of the first paper strips. A drop of blood was placed on the paper strip for one minute and then washed off. In the 1978-1980s, portable home glucose meters came to the market. These devices allowed patients with diabetes to monitor their blood glucose levels for the first time. This was the first true blood glucose monitoring method available and, from a medical point of view, it allowed a therapeutic approach based mainly on insulin administration. Called "Self-Monitoring of Blood Glucose" (SMBG), this solution is now the most widely used technology by diabetic patients to monitor their blood glucose levels [64]. Using a blood glucose meter (glucometer), the patient performs a number of daily or weekly tests by taking a small sample of blood using a "finger prick" method, which is uncomfortable, inconvenient and leads to poor patient compliance [12, 65, 66]. This system allows patients to some extent to manage their insulin levels through self-monitoring of blood glucose (SMBG). However, these tests do not take into account changes in blood glucose levels during the night. They are therefore unable to provide advance warning of hypoglycemic (< 3.0 mM) and hyperglycemic (> 11.1 mM) events [67, 68]. Furthermore, the self-monitoring of blood glucose cannot provide the trends, direction and frequency of blood glucose

changes that are important information for physicians. For these reasons, research has focused on the development of new testing approaches capable of providing continuous glucose monitoring. Achieving continuous glucose monitoring directly in the blood appears to be very complicated because blood glucose monitoring has a high risk of infection.

3.2.2. Interstitial fluid

The detection of glucose in the subcutaneous (SC) interstitial fluid (ISF) has emerged as a promising solution for the development of CGMs [69, 70]. The existence of a correlation between the level of glucose in the ISF and glycemia makes it possible to develop CGMS using less invasive systems. In 1999, the US Food and Drug Administration approved the first "professional" CGM. The introduction of real-time CGMs was a breakthrough in the treatment of diabetes. Since that, many attempts have been made to assess the relationship between blood glucose and interstitial fluid glucose (IFG) levels. The focus has been on assessing a delay between blood and ISF readings, and the impact of insulin on the glucose gradient from plasma to ISF. Some studies reported that the time between blood and ISF readings was less than 10 minutes, whether glucose was rising or falling, and that the plasma to ISF glucose gradient was stable [71, 72]. Other studies have shown long delays that differ between rising and falling glucose and have argued that there is a marked effect of insulin on the plasma-ISF gradient [73].

While glucose measurement in the ISF is the most widely used strategy for continuous glucose monitoring, there is a lot of ongoing research into new, completely non-invasive approaches, since subcutaneous glucose detection requires the use of invasive electrodes, which are not entirely comfortable and can lead to skin complications [74, 75].

3.2.3. Sweat

Sweat is also an important body fluid for non-invasive sensors that reflect the physiological state of the body in real time. Sweat glands are present throughout the body and glucose from the interstitial fluid easily diffuses into the sweat, allowing simply measurement of its concentration by collecting fresh sweat. Sweat glucose level (SG) has been successfully investigated [76–79]. A. Karyakin et *al*. [80] showed a positive correlation between the rates of change of blood glucose in sweat and blood in a group of 19 healthy human volunteers and the results clearly showed a positive correlation between the rates of change of blood glucose in sweat and blood. The detection of glucose in sweat using machine learning to monitor blood glucose continuously was studied by Shalini Prasad et *al*. [81–83]. According to the authors, the data-driven machine learning approach showed promising results when tested on three healthy subjects. Despite this encouraging work, the correlation with blood glucose (in terms of concentration and latency) needs to be more studied and clarified before it can be used as a blood glucose monitoring tool. In addition, there are many other technical issues that need to be addressed i.e.: operating conditions that affect sensor response, such as pH and temperature [84], are not constant, contaminants remain on the skin, sweat evaporation rates are not constant, and old and new sweat is always mixed which may affect the measurement.

3.2.4. Tears

Tears secreted by the lacrimal glands also contain glucose and some electrolytes, and the concentration of glucose in tears (~ 0.5 mM) is known to well-correlate with blood glucose [85, 86]. The challenge is to collect enough tears to measure glucose. A pioneering achievement was the development of an electrochemical sensor in which the enzyme Glucose oxidase (GOx) was immobilized on an electrode formed on a plastic film [87]. Later, contact lens-type tear glucose sensors emerged, which are relatively easy to wear and are less burdensome for the user [88–91]. This type of electrochemical sensors combines an antenna for electromagnetic induction power and a data transmitter. However, difficult sampling procedures complicate reliable tear-based sensing platforms, while contact lens systems suffer from design constraints imposed by the nature of their operating environment.

3.2.5. Saliva

Saliva is a body fluid that can be easily collected and is suitable for assessing health status [23]. With regard to glucose detection, it is known that there is a correlation between the concentration of glucose in saliva and the level of glucose in blood [92–94]. Although the concentration of glucose in saliva is much lower compared to the level of glucose in blood, it is feasible to determine blood glucose levels in diabetic patients. However, it is difficult to measure the low concentration of glucose in saliva with high sensitivity, and measurement is also affected by the presence of high concentrations of many bacteria in the oral cavity [95]. Recently, a portable mouthpiece-type sensor with a wireless transmitter has been developed that can measure glucose concentrations from 0.05 to 1 mM [96]. In the future, the development of miniaturized and more biocompatible devices is expected [97–101], especially in term of power supply, which may lead to enhance the monitoring of glucose in saliva.

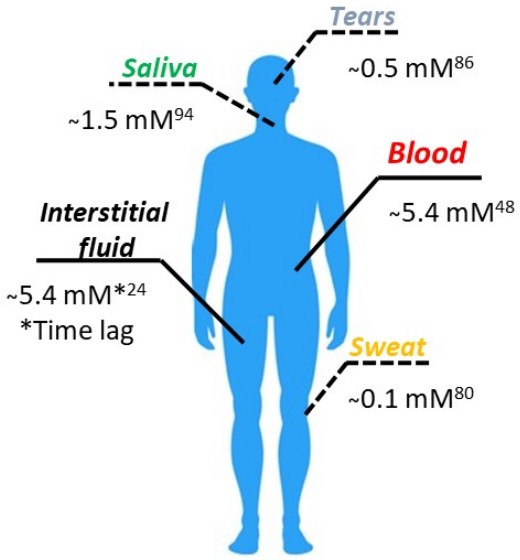

Figure 3. Potential glucose measurement sites with the mean expected value for normal fasting blood glucose concentration.

4. Principles of glucose sensing

4.1. Description of biosensor components

A biosensor is an analytical device designed to transform a biochemical phenomenon into a measurable signal. It integrates two main components [102, 103]: (1) a biological component called a "bioreceptor" to recognize a target substance in a complex medium, and (2) a physical transducer to translate the physico-chemical changes (e.g., photon emission, pH change, mass change) resulting from the recognition of analyte into a measurable electrical signal (for electrochemical biosensors) that can be correlated to the concentration of the target substance in the medium. The various components of a biosensor are described in Figure 4A. Depending of the detection mode (light intensity, heat and electric current…), there are different types of transducers, such as optical [104], thermal [105] or electrochemical [106]. Nowadays, the signal is finally collected, amplified, and displayed by an electronic processor to quantify the target substance.

In glucose enzymatic sensors, the bioreceptors usually used are enzymes Glucose Oxidase (GOx) or Glucose Dehydrogenase (GDH) [107, 108] (Figure 4B). Other receptors of the glucose sensor are based on glucose-specific proteins such as Con-A [109] or may be abiotic like metal or metal oxide nanostructures and their composites [110, 111]. The transducer can be either optical, electrochemical, mass-based or thermometric [112]. The following sections describe the electrochemical and optical biosensors in detail.

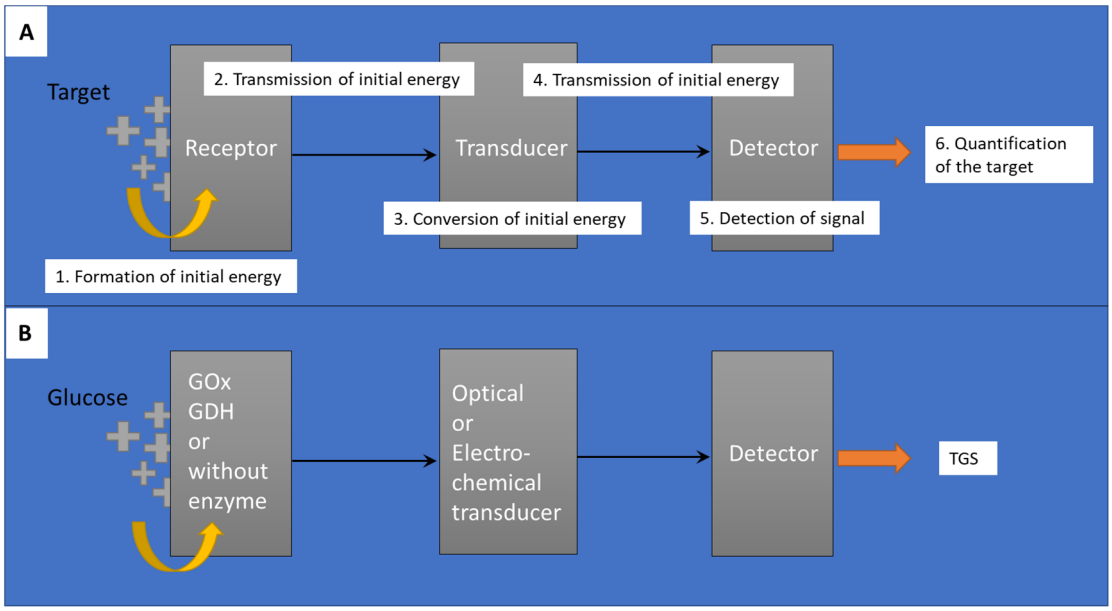

Figure 4. (a) General description a biosensor component and (b) description of the glucose biosensor detection strategy.

4.2. Electrochemical enzymatic glucose sensor

Electrochemical biosensors have electrodes that transform a chemical signal into an electrical signal. Most biosensors use electrochemical sensing as a transducer because of its low cost, ease of use and construction, and portability. The electrochemical reaction generates either a current (amperometry), a potential (potentiometry) or a change in the conductivity of the medium between the electrodes (impedance and conductimetry) [113]. Electrochemical sensors consist of either three electrodes (a working/sensing electrode, a reference electrode and an auxiliary electrode) that usually refers to amperometric sensors [114] or two electrodes (working/sensing and pseudo-reference electrodes) if the current density delivered by the electrochemical reaction is sufficiently low (a few $\mu A.cm^{-2}$) that usually refers to potentiometric sensors. For disposable sensors, two-electrode systems are generally preferred because long-term stability of the reference is not required and it could be a source of cost reduction [115].

Self-Monitoring of Blood Glucose (SMBG) strips are amperometric enzymatic sensors based on a measurable amount of current generated by electrochemical reaction at a fixed potential maintained at the working electrode. The current is directly proportional to the concentration of the electroactive species in the matrix, allowing the establishment of a calibration curve ($i_{(A)} = f[analyte]_{(mol.L^{-1})}$) and the determination of the biosensor sensitivity (which corresponds to the slope value and are expressed in current $A/mol.L^{-1}$). In many SMBG, the signal is averaged during 5 seconds to improve signal to noise ratio and accuracy.

The primary goal of glucose sensors used in diabetes care is to detect hyperglycemia, i.e., glycemia above 120 – 150 mg/dL or 7 – 9 mM depending on the type of diabetes. The demand for accurate glucose measurements in order to manage diabetes has been summarized in the Clark Error Grid that is an essential tool for checking the clinical accuracy of self-monitoring of blood glucose monitors [116, 117]. Biosensor accuracy in the 3 – 10 mM is therefore the primary need. The detection limit of biosensors is usually defined as the lowest concentration of the target that is able to elicit a measurable signal or response. However, a low detection limit is clearly not the primary target in glucose sensor development.

The enzymatic glucose sensors are well-described in the literature. Briefly, they are categorized into three types: first, second or third generation [5, 16, 118–120]. In the first generation, the byproduct of the enzymatic reaction, hydrogen peroxide (H_2O_2), diffuses to the transducer and generates the electrochemical response. However, this type of biosensor typically requires high polarizing potential

where other species present in the blood (e.g., ascorbic acid) can also be oxidized, and is limited by the oxygen supply in the tissues [121]. To overcome this, researchers worked on modifying the surface of electrodes by using Prussian blue (PB) that is known to catalyze H_2O_2 reduction near to 0 V *vs* Ag/AgCl (- 0.1 V ± 0.05 *vs* Ag/AgCl) [122–124]. This strategy allows to avoid electrochemical interferences at high polarizing potentials. Two options are typically available for the electrode's modification by PB: by using electroplating process or by screen-printing technique [125]. However, the stability of PB remains the main limitation for its use. Many authors reported a loss of sensitivity of PB-based electrodes, especially at high concentrations of H_2O_2 (few mmol.L^{-1}) probably due to the degradation of PB on the electrode interface over time [126–128]. Indeed, PB remains a good option for the development of a disposable glucose sensor but its limitation in long contact with H_2O_2 is not applicable for one-use sensor. Another strategy was recently reported in the literature to lower the detection potentials of H_2O_2, is to use Ruthenium Purple (RP) as an alternative to the PB material that seems to present better stability over time [129–131].

In the second generation of biosensors, electron transfer between the enzyme and the transducer is provided by intermediate compounds, called mediators, immobilized together with the enzyme on the surface of the electrode [132, 133]. Quantifying glucose is equivalent to quantifying the oxidation of the mediator at the electrode surface. However, the small size of the mediator and its usually non-covalent incorporation favors their diffusion, which reduces their catalytic activity. They can also compete with naturally occurring oxygen, which in most cases avoids an oxygen interference reaction. Indeed, from the list of chemical species, ferrocene derivatives [134], ferricyanide, quinone compounds and transition-metal complexes are of particular interest for second generation glucose biosensors [135–139].

In the case of the third-generation biosensors, direct electron transfer is possible between the active site of the enzyme and the transducer, and the enzyme-catalyzed glucose oxidation current is measured directly at the electrode surface [101, 140–142]. The reaction itself causes the response and no product or mediator diffusion is directly involved.

However, implantable electrochemical glucose sensors face two major problems: loss of sensitivity over time and the short lifetime of immobilized enzymes (up to 14 days) [143, 144]. The loss of sensitivity implies either a replacement or a regular calibration of the sensors. Indeed, enzyme immobilization and enzyme cross-linking are common strategies allowing the design of biosensors with enhanced stability over time [145, 146]. Enzyme entrapment or encapsulation in a biocompatible polymers or hydrogel-based matrices (e.g.: chitosan [147, 148], cellulose[149], collagen [150], etc.), is one of the most popular immobilization methods used in designing enzymatic biosensors and play a key role in the stability of enzymes. On the other hand, Zimmer and Peacock (ZP) has data that says that glucose oxidase is extremely robust, the reasons why implanted sensors have problems is encapsulation. It is crucial that physical and chemical proprieties of these matrixes are well-designed to enhance the stability of the glucose biosensor over time.

4.3. Optical glucose sensor

Optical measurement methods are already used in medical monitoring, diagnosis or treatment, and have also attracted great interest in the development of glucose sensors [104]. The short measurement time and long sensor lifetime are the main advantages of optical sensors over electrochemical sensors, and can be a game changer in the field of CGM [151]. In general, optical sensing is based on different forms of light-matter interaction such as absorption, emission, scattering, reflectance, fluorescence, etc. So far, many techniques have been proposed for glucose detection, such as infrared [152, 153] and Raman spectroscopy [154], surface plasmon resonance [155], chemiluminescence or fluorescence [156–158]. Despite the many advantages and possible solutions, only one optical CGM (Eversense from Sensonics) is currently commercially available and uses fluorescence as its operating principle. The concern with Eversense is that the patients are required to test their blood twice a day in order to recalibrate the sensor.

Fluorescence is a phenomenon related to the excitation of a molecule by a photon absorption and its subsequent return to the ground state by emission of lower energy photon. Such process can be

monitored by the emission of light from optically excited molecule, which is characteristic for specific chemical groups, compounds and structures. Moreover, emission intensity and fluorescence lifetime depend on the environment of the excited molecule [159, 160]. The molecules for which fluorescence is observed are called fluorophores, however glucose does not belong to this group. Thus, for its detection glucose is combined with fluorophores such as enzymes, dyes, conducting polymers, carbon nanotubes/quantum dots and others. Due to the interaction between glucose and fluorophores fluorescence intensity changes upon glucose binding, and the concentration of glucose can be quantified [161]. However, in most cases, the mechanism of the fluorescence sensing is more complicated and uses an indirect interaction of glucose via receptors. The receptors are attached to the fluorophore and can bind glucose reversibly. Examples of receptors are enzymes (glucose oxidase, glucose dehydrogenase, hexokinase), glucose-binding proteins (Concanavalin A, a bacterial glucose-binding protein used by Lifecare AS Norway) and boronic acids derivatives [162]. Binding of glucose to the receptor leads to the quenching or increasing fluorescence due to the energy transfer. Schematic representation of a receptor-based glucose sensor is presented in the Figure 5. The same principle is used in the commercially available optical CGM (Eversense from Sensonics), in which the indicator hydrogel is a boronic acid derivative acting as a glucose receptor and a polymer as a fluorophore. In the absence of glucose (unbound receptor), emission from the excited fluorophore is quenched by intermolecular electron transfer from the unoccupied receptor. Interaction with glucose induces a change in the redox/ionization state of the receptor, preventing electron transfer to the fluorophore and fluorescence quenching (Figure 5) [160]. The intensity of the fluorescence increases with the number of bound receptors, corresponding to the increase in glucose concentration.

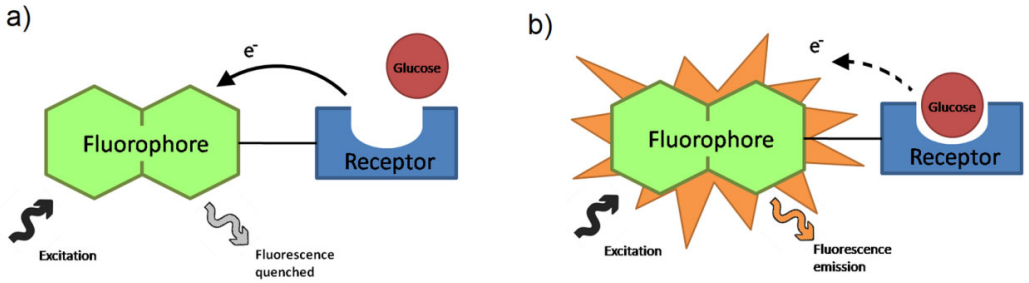

Figure 5. Schematic representation of a receptor-based fluorescence system used in optical glucose sensing.

5. Continuous Glucose Monitoring systems (CGMs)

5.1. The added value of CGMs

Point-of-care (POC) devices were the first to emerge on the market and are based on traditional test strips [163]. They are used with handheld meters, use a drop of blood to determine the glucose level and allow patients to self-monitor. However, in such an approach, the glucose level is not quantified continuously but at frequencies proposed by clinician according to the patient acceptance. In addition, repeated measurements are inconvenient and painful. Self-monitoring of glucose levels was revolutionized a few years ago with the introduction of continuous glucose monitors [164, 165]. The unique feature of these devices is that they continuously measure and store glucose levels with sampled readings on a frequent and repetitive basis, the storage being data accumulated over 5 – 15-minutes periods. They are used as invasive implants or non-invasive devices (see section 3.3) and are equipped with an alarm to warn the patient of hypo- or hyperglycemia. Obtaining a blood glucose trend is then easily achievable.

The use of CGM has been shown to enhance glycemic control, reduce blood glucose variability and, prevent hypoglycemia risk [166, 167]. Furthermore, the higher the patient's HbA1c, the more beneficial the use of CGMs is for the patient [118]. More recently, smart technologies using algorithms (artificial

intelligence) were involved to be connected to CGMs and insulin pump in a closed-loop system allowing an automatic insulin administration by the pump driven by the algorithm [168–170].

5.2. Personal and professional CGMs

There are two main families of continuous measurement devices [171–173]: personal and professional CGMs. Personal CGMs are useful for diary therapy administration and allow access to information and determination of blood glucose levels in real time. In addition, the CGM is equipped with a configurable alarm system that alerts the patient to very high or very low glycemia. The professional CGMs are useful for retrospective study of data by a professional of healthcare. The glycemia is measured continuously but the values are recorded and not transmitted in real time.

5.2.1. Personal CGM

The personal CGM is used by the persons with T1D and T2D [174], as well as pregnant women who are exposed to gestational diabetes [175]. In general, it is intended for people who are at high risk of hypoglycemia, and who need to monitor their blood glucose levels continuously. It allows the patient to self-manage their diabetes therefore without the need for repeat capillary blood glucose samples. On a daily basis, the personal CGM can be used to monitor its glucose level and to alert the patient in case of exposure of a severe hypoglycemic episode and abnormally high glycemia after a meal (hyperglycemia) [118, 176].

The personal CGM has demonstrated to improves blood glucose monitoring, reduces day and night-time hypoglycemia, prevents impending hypoglycemia and hyperglycemia and avoids severe hypoglycemia. Another new approach may improve diabetes management at the personal level: coupling a CGM with an insulin pump [20, 168–170]. A step towards such an artificial pancreas is achieved with these augmented sensor pumps (SAP), which can stop preventively the insulin infusion if the patient is at risk of hypoglycemia. This reduces the risk of hypoglycemia.

However, the use of personal CGMs is not always successful with people with diabetes. Indeed, 40% of users return to an older blood glucose monitoring system due to: (1) the high cost of CGM devices, (2) the frustration of using a new technology (the patient must have full confidence in the accuracy and reliability of the sensor), (3) hardware constraints (the devices may be inconvenient for the user), and (4) frequent alarms causing stress for the user.

5.2.2. Professional CGM

The professional CGM is mainly used in hospitals to monitor patients' ambulatory blood glucose levels. There are three main applications of professional CGMs [177, 178]:

- Diagnosis issue;
- Establishment of the suitability of the patient for the treatment and the device, conduct pharmacodynamic studies;
- Adjustment of therapy to best treat the patient, compare treatments by comparing glycemic variability (GV), and visualization of nocturnal glycemic variations and postprandial patterns.

Thus, professional CGMs do not deliver BG in real time to the patient, but provide glycemic profiles throughout the day (after meals, after taking medication, etc.) for data collection and further analysis by professionals. In order to make a good adjustment of a therapy, it is necessary to obtain typical daily glycemia profiles. According to the research, the estimated follow-up time per professional CGM should be at least two weeks [179]. After this time, GV can be defined and a stable trend in the ambulatory glucose profile is obtained. Retrospective analysis thus allows the detection of postprandial hyperglycemia and unknown day or night hypoglycemia.

Professional CGMs are thus broadly used in clinical research, thanks to advantages such as accuracy, ease of use, short duration of use, good degree of acceptance, low cost, previous conclusive studies. Its

characteristics have considerably improved the ambulatory follow-up of glycemia, previously taken with a POC device, on an empty stomach and for up to 8 time points over one to three days (i.e., a glucose profile carried out using 8 capillary measurements per day). Indeed, the professional CGMs is less expensive compared to the personal CGM. It does not require a real-time data transmission module (no receiver) and the transmitter belongs to the hospital. However, the sensor remains disposable. The only additional costs are those related to the interpretation of data by medical staff. However, the interpretation of the results by a professional has a greater impact on the patient: he/she can become aware of the effects on his/her body requirements or daily nutrient intake and physical activity [180]. Thanks to the support of the medical staff, they gain more confidence with the device than with a personal CGM. Professional CGM devices have proven to be indispensable for patients unable to manage the information provided by personal CGMs. In addition, professional testing can determine whether HbA1c levels are relevant for blood glucose assessment and generate treatment options, which is not possible with personal CGMs.

5.3. Difficulties in setting up

The implementation of CGMs faces difficulties from different sources [166, 181]:

(1) Difficulties related to detection: a time delay exists between the concentration of glucose in the blood and in the interstitial fluid (5 – 10 min). An abnormal blood glucose level is detected with delay and is detectable in the interstitial fluid while the glycemia is normal;

(2) Difficulties related to patient education: CGMs are new devices that need to be explained to users (patients and professionals). Interpretation of the results by the patient is essential for them to adapt their therapy and lifestyle. Patient education is also an issue to overcome the lack of user confidence in this new technology;

(3) Difficulties related to the universalization of sensors: defining a standard for control algorithms and critical thresholds is difficult;

(4) Difficulties related to the lack of sensor stability: electrochemical biosensors are enzymes-based sensors detecting and quantifying glucose. Optical sensors suffer also from the same technical issue which requires a daily calibration or to change the sensor.

(5) Short lifetime (replace after 14 days).

5.4. Consensus-appropriate patient selection

There is a consensus to standardize the use of the GCMs and proposed four main cases which require their use [179, 182–184]: (1) Cases of frequent severe hypoglycemic episodes, severe nocturnal hypoglycemia and/or hypoglycemic unconsciousness; (2) cases of poor metabolic control if, despite the application of various forms of therapy, HbA1c levels are unsatisfactory; (3) cases of pregnancy if metabolic control is poor despite various more conventional treatments; and (4) cases where more than ten daily blood glucose readings are required to achieve good HbA1c levels.

Thus, CGMs are not recommended if: (1) The patient lacks motivation and compliance with treatment; (2) the patient fears these systems or does not have sufficient confidence in them; (3) the patient abuses drugs or alcohol; and (4) the patient has psychological problems such as bulimia, anorexia or psychosis.

The use of the CGM includes different requirements: (1) Healthcare professionals' selection of patients for CGM based on compliance, absence of contraindications, absence of other functional treatment; (2) participation in training; (3) the patient must be supervised by a diabetologist trained in CGM; and (4) the patient must go through a trial period to validate effectiveness of treatment.

5.5. Review of the main commercial CGMs

The first CGM system (Minimed) was approved by the FDA (Food and Drug Administration) in 1999 and since then considerable progress have been made in both sensor development and availability [173, 179]. Only in the fourth quarter of last year more than 1,5 mld USD was spent for CGMs (with *Dexcom Inc*. as the main player on the market). Currently, four companies commercialize FDA-approved CGMs systems that can be listed as: Dexcom Inc. [185–187], Medtronic [188, 189], Abbott Laboratories [190] and Senseonics [191, 192]. All of them are indicated for monitoring of glucose level in the interstitial fluid under the skin, across the claimed measuring range from 40 to 400 mg/dL glucose. First three propose electrochemical glucose sensor, with typical enzyme of glucose oxidase-based sensing. They are subcutaneous devices employing micro-needle sensors which can be classified as an invasive sensor (usually also called minimally-invasive). For the correct determination of the glucose values, sensors have to be used at the approved application sites (typically upper arm or abdomen). On the other hand, Eversense recently introduced by Senseonics is an implantable optical sensor. The proposed solution is an abiotic system, which is based on fluorescent detection.

Besides principle of glucose detection and insertion procedure, available CGMs differ in senor lifetime, accuracy and calibration requirements. All the systems are compatible with mobile application and offer additional functions such as alerts for hyper- and hypo-glycemic level or prediction of glucose trends. In most systems, data are automatically sent to the receiver and displayed immediately after measurement (note that this technology is sometimes referred to as real-time CGM). Moreover, some CGM systems can be integrated with insulin pumps and create artificial pancreas with automatic insulin adjustments.

In this review, only the newest models of personal CGMs from each company were discussed. Table 1 presents the comparison of CGMs, discussed in this paper, with respect to their operational parameters such as working principle, accuracy, sensor and transmitter lifetime, calibration requirements or available alarms [193]. Herein, accuracy was defined in term of the Mean Absolute Relative Difference (MARD, %), which is commonly used in the glucose sensing community. Lower MARD values indicate better accuracy [194]. It is based on the comparison between paired measurements of a given CGM system and a reference method. MARD is computed as mean value of the absolute relative differences (ARD) where y_{CGM} is the value measured by the CGM device, y_{ref} is the value measured by the reference measurement device at t_k where t_k, k = 1, 2, …N_{ref} are the times when reference measurements are available [195]:

$$ARD_k = 100\% \times \frac{y_{CGM\,(t_k)} - y_{ref\,(t_k)}}{y_{ref\,(t_k)}}$$

$$MARD = \frac{1}{N_{ref}} \sum_{K=1}^{N_{ref}} ARD_K$$

Table 1. Comparison of discussed CGMs: the newest model from companies with FDA approval.

	Dexcom G7 ® (*Dexcom Inc.*) [196]	**Guardian Sensor 4 (GS4)** ® (*Medtronic*) [197, 198]	**Freestyle Libre 3**® (*Abbott*) [199, 200]	**Eversense E3** ® (*Senseonics*) [201, 202]
Detection principle	Electrochemical enzyme-based glucose oxidase / dehydrogenase			Optical
	1st generation		2nd generation	Fluorometry
Type	Invasive (also categorized as minimally-invasive) with subcutaneous sensor			Implantable / Invasive

Insertion	Upper arm and abdomen for ages 2-years and older or the upper buttocks for ages 2-17 years old Self-inserted	Abdomen or upper arm Self-inserted	Upper arm Self-inserted	Upper arm, placed in healthcare provider's office through a small incision (10-min procedure)
Sensor lifetime	10 days	7 days	14 days	90 days in US and up to 180-days in Europe
Transmitter lifetime	3 months	12 months	14 days *	12 months
Accuracy (MARD%)	8.2 % to 9.1 %	8.7 % to 10.6 %	7.6 % to 8.7 %	8.5 % to 9.1 %
Glucose reading frequency	5 minutes	5 minutes	1 minute	5 minutes
Calibration protocols according to the providers	No, Factory-calibrated **			4 at the first day and then 2 per day, using fingerstick readings from a BG meter
Warm up period (hrs)	0.5	2	1	24
Glucose alerts	Audible, customizable alarms: low, high, urgent low prediction (20 min). Mandatory urgent low alert (below 55 mgl/dL)	Audible, customizable alarms: low, high, rate, predictive (10 to 60 min) and mandatory Urgent Low Alert (below 55 mg/dL)	Audible or on-body vibe alerts for high and low glucose level	Audible or on-body vibe alerts, mandatory low and high alarms, optional predictive alerts (10, 20, 30 min)

* No additional transmitter combined with the sensor.
** The user does not have to do any calibration prior to use. The sensor current has been pre-determined against *in vitro* glucose levels and is corrected according to the sensor's evolution over time.

5.5.1. Dexcom G7 (from Dexcom Inc.)

Dexcom G7 was approved in Europe in 2022. This is the Seventh-generation version of Dexcom's 'G' series CGM. Like its predecessors, the Dexcom G7 sensor is based on electrochemical glucose detection. It relies on a subcutaneous glucose oxidase-based sensor that is factory calibrated and allows for optional user-initiated calibrations [196]. The MARD reported by the manufacturer is about 8.2 % to 9.1 %.

Comparing of Dexcom G7 to its predecessor Dexcom's mainstay G6 sensor, which made its debut in 2018, the Dexcom G7 is designed to be discreet, all-in-one wearable sensor, and 60% smaller than the sixth-generation (Figure 6). It is composed of sensor wire and transmitter, which is placed on top by plastic holder. Users insert the sensor wire under the skin by themselves, with the single-use auto applicator. The system is inserted in the upper arm and abdomen for ages 2-years and older or the upper buttocks for ages 2-17 years old. The glucose sensor life is 10 days, while transmitter can be-reuses for maximum of 3 months [185–187].

The wearable transmitter measures 2.4 × 2.7 × 0.46 cm (Figure 7). It sends ISF glucose levels to the display device (a smart device or dedicated receiver) every 5 minutes via Bluetooth. The patient receives current glucose readings and trends. This data can be also shared with up to 10 followers. Alerts inform the user when the glucose levels or rates of change are outside of a target zone and when other important

system conditions occur i.e., when the glucose level falls to 55 mg/dl or below (‘urgent low' alert, cannot be deactivated), or if the glucose level is predicted to drop to 55 mg/dl within 20 minutes ('urgent low soon'). In addition, the Dexcom apps and software are compatible with wide-ranging number of devices and platforms i.e.; insulin pumps: the Diabecare R (DANA) or the Tandem t: slim X2 (Tandem), etc.

Figure 6. Size evolutionary of Dexcom G6 to G7 wearable transmitter (adapted from Dexcom website: https://www.dexcom.com/).

5.5.2. Guardian Sensor 4 (from Medtronic)

Medtronic released the Minimed in 1999 being the first company to introduce the CGM to the market. This historical device recorded glucose value for 3 days, however, data could only be downloaded at healthcare’s office and analyzed by physician (“professional” CGM). Last year (in 2021), their newest Guardian Sensor 4 CGM system secured two CE (European Conformity) mark approvals. Similar to Dexcom, Guardian™ Sensor 4 CGM system uses a subcutaneous wire-based, first-generation electrochemical sensor [203]. Medtronic’s reported MARD range from 8.7 % to 10.6 % depending on age, insertion place and quantity of calibrations. Most accurate measurement can be obtained with 3 to 4 calibrations per day for patient older than 14 years with sensor inserted on the upper arm [197, 198].

The dimensions of the sensor with transmitter are approximately 3.6 x 2.9 x 1.0 cm and weight around 1 g (Figure 7). Sensor 4 GM can be easily inserted by the user with a single press of an applicator button. The transmitter is connected via a special pod and the area is covered with an adhesive. Guardian™ sensor 4 system is suitable for patients aged 14 to 75 years of age and is inserted in the abdomen or upper arm. It can be worn up to 7 days and requires minimum 2 calibrations each day to ensure the accuracy of the device. The transmitter with 12-month warranty is rechargeable and needs to be charged every 6 days.

ISF glucose levels are measured every 5 minutes and the readings are sent to a smart device via Bluetooth. The mobile application displays user’s current glucose level and indicates rate of its change with an arrow. Customizable alarms can be set for different glucose threshold and timeframe, “urgent low glucose” alerting when the glucose level falls below 55 mg/dL is also available. Moreover, the system also comes with predictive alerts that notify users from 10 up to 60 minutes before high or low blood glucose level is expected.

The Guardian™ sensor 4 system is designed to be connected to InPen which is the first and only smart insulin pen approved in Europe that is integrated with a CGM in real-time via one convenient smartphone application [204]. The MiniMed 780G system can also be integrated with Guardian™ 4 sensor and will automatically adjust insulin for patients who prefer automated insulin delivery via a fingerless insulin pump [205–207].

5.5.3. FreeStyle Libre 3 (from Abbott)

In 2020, Abbott obtained approval for the FreeStyle Libre 3 in Europe and two years later (in 2022) was approved in the US and is now cleared by FDA. Contrary to the previous generation (FreeStyle Libre 1 and 2), Freestyle Libre 3 does not require that users pass receiver over the sensor in order to get the glucose reading. The data are automatically transmitted to the reader or to the patient's phone application. Another difference is the generation of electrochemical glucose sensing principles where FreeStyle Libre 3 uses a second-generation electrochemical process in which a redox mediator transport electrons from the glucose oxidase enzyme to the surface of the sensing electrode [75, 208].

The sensor weights 1 g and has rounded shape with 2.1 cm diameter and 0.29 cm height (Figure 7). It incorporates both the subcutaneously implanted filament-based sensor and the transmitter part. It is designed to be the smallest, thinnest, and most discreet glucose sensor now available on the market. It can be worn for 14 days requiring no calibration, making it the longest lasting CGM sensor available [209]. Its MARD is about 7.6 % to 8.7 [199, 200]. Sensor is inserted under the skin using easy applicator, and it is approved for use only on the upper arm and above 4 years old.

The sensor measures interstitial glucose level continuously and automatically delivers real-time, minute-by-minute glucose readings to the user's smart device. In case of notification, real-time alerts (sound or vibration) are viable informing only about low or high level of glucose (threshold set by the user). It also gets permission to be used as part of an integrated system with other compatible medical devices such as automated insulin dosing systems or insulin pumps.

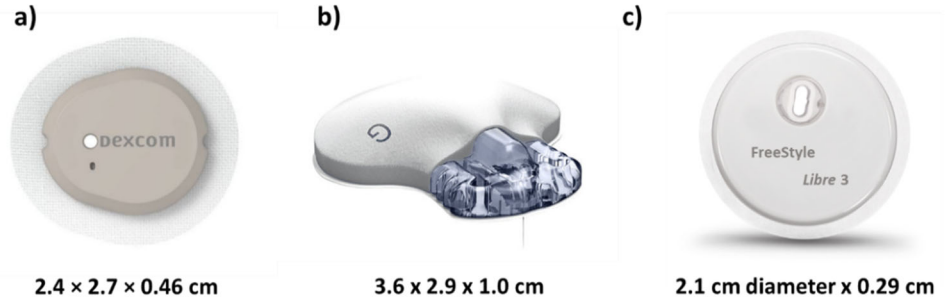

Figure 7. Images of CGMs based on micro-needle sensors with their dimensions: (a) Dexcom G7, (b) Guardian Sensor 4, and (c) FreeStyle Libre 3.

5.5.4. Eversense E3 (from Senseonics)

Senseonics got into the game in 2016 (2018 in USA) with its unique implantable long-term CGM-Eversense. Recently, Senseonics received the CE Mark approval for its Eversense E3 in Europe are available since mid-2022 on the European market. Compared with other approved CGM systems, Eversense E3 is non-enzymatic, fluorescent based-sensor for glucose detection. The sensor is an abiotic-system with indicator hydrogel, which is based on selective, fully reversible binding between glucose and the covalently attached molecular complex. According to the regulatory approval it is indicated for continually measuring ISF glucose levels in adults (age 18 and older, non-pregnant) for up to 90 days in the US, and 180 days in Europe. Its MARD (%) is about 8.5 % to 9.1, which makes it part of the most accurate CGM on the market. However, fingerstick glycemia measurements are still required for calibration primarily one time a day after day 21, and when symptoms do not match CGM information or when taking medications of the tetracycline class [191, 192].

Currently, Eversense E3 is the only CGM system with an implantable sensor, completely inserted under the skin, leaving no part of the sensor protruding as it is in case of other available CGMs [201, 202]. Insertion (upper arm) and removal are carried out by a healthcare provider, within approx. 5-minutes procedure and a small incision (less than 1 cm). The diameter of the tubular sensor is approximately of 0.35 cm and length equal 1.83 cm. Moreover, it has a silicone ring that contains a small amount of

dexamethasone acetate in order to minimize inflammatory responses (Figure 8). There are concerns of patient acceptance as the insertion has to be performed by a medical professional and this in conjunction with the requirement of testing twice a day with an SMBG strip could limit market penetration.

The sensor activated by radio frequency power (RF) from transmitter, measures glucose level every 5 minutes and sends data to the transmitter. External transmitter (length: 3.7 cm, width: 4.8 cm, thickness: 0.89 cm, mass: 11.3 g) must be placed directly over the sensor and it is secured on the skin with the disposable adhesive patch. However, once per day it needs to be recharged for about 15 minutes, and then re-attached to the arm with new adhesive. Besides powering the sensor, transmitter calculates, stores, and transmits the glucose data via Bluetooth to the mobile device. It has 1-year limited warranty [201, 202].

The same as for previously described CGMs, the Eversense App displays glucose measurements, rate and direction change and graphics trends of glucose levels. Besides audio notification, transmitter on-body vibe alerts are available. Low and high alerts cannot be turned off, targets can be set within allowable range. Optional predictive alerts let user know in advance (10, 20, or 30 minutes) that a high or low glucose event is likely to occur if current trends continue [210]. The device is being designed as stand-alone CGM and it does not integrate at this time with an insulin pump.

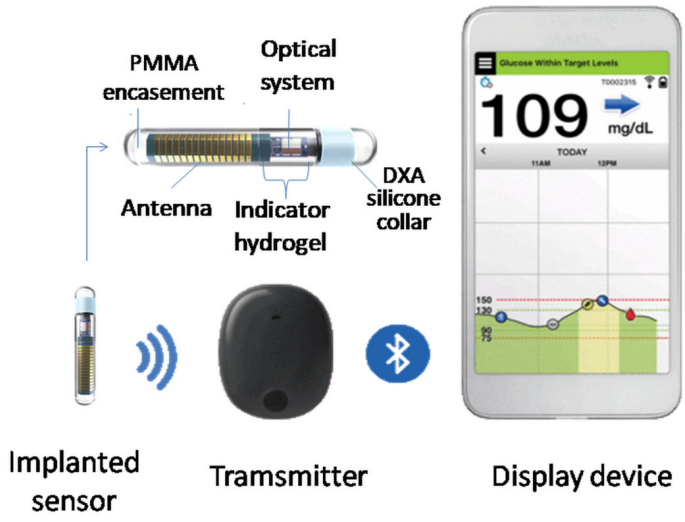

Figure 8. Elements of Eversense® CGM: implantable sensor, transmitter and connected device (adapted from Senseonics website)

5.6. The future of CGM systems: challenges and prospects

As mentioned earlier, CGMs have been developed to extrapolate back from the glucose levels in the interstitial fluid (ISF) to the blood glucose levels. These monitors are now commercially available on the market from different manufacturers (Dexcom, Medtronic, Abbott, etc.). Non-invasive devices (e.g.; wearable glucose sensors) have clear advantages over invasive or minimally-invasive devices [211]. Patient compliance, i.e., patient acceptance of the device, may greatly be facilitated. Various non-invasive wearable devices are being developed [193, 212–216] but are not yet commercialized until now. Indeed, these devices are external to the body, it is expected that they face less biocompatibility complications and better/longer lifetime. However, accuracy is more difficult to achieve. These sensors aim to measure glucose concentrations in body fluids, such as tears, sweat, saliva, and urine; these fluids can be easily collected without inserting a needle into the skin and are not affected by inflammation. One common issue in the sensing of such body fluids is the correlation between blood glucose levels and time delay (5 – 10 min). The new, easy-to-use, wearable glucose sensors are expected to lead to a new type of glycemic control in the future.

On the other hand, improvement of the invasive or minimally-invasive devices especially in terms of accuracy and sensor lifetime are expected to be the subject of many enhancements in the upcoming year. Also, the integration and association of these devices within insulin pumps and functioning in closed loop system [217] that leads to automatize insulin injection, are expected to be generalized as artificial pancreas [218, 219].

6. Wearable biosensors

Wearable biosensors (WBSs) are wearable electronic devices that incorporate biosensors located on the skin or in the human body in the form of patches, tattoos, gloves, clothing and implants [214, 220]. These devices allow for *in vivo* sensing, data recording and computation using mobile or wearable devices (Figure 9). In addition, these devices allow the non-invasive, real-time quantification in body fluids such as saliva, sweat, skin and tears of various biochemical markers for the diagnosis of diseases such as diabetes, obesity, heart disease and hypoxia [221, 222]. For continuous glucose monitoring, sweat seems to be more suitable. Indeed, sweat is an important body fluid for non-invasive sensors that may reflect the physiological state of the body in real time. Sweat glands are present throughout the body and glucose from the interstitial fluid easily diffuses into the sweat, allowing simply measurement of its concentration by collecting fresh sweat (check § 3.2.3). Even though, many studies showed that it is possible to monitor sweat glucose via wearable glucose biosensors, many issues need to be overcome a successful commercial. Some of these issues are due to limited fundamental knowledge of sweat composition and how it connected to physiological parameters and health state. This is not really surprising especially in the case of sweat where the acquisition of such knowledges requires a tool that allow continuous monitoring of sweat glucose in healthy and diabetes peoples [223] and from this point of view, one of first application of wearable glucose biosensors may be the investigation of the evolution of sweat glucose and its correlation with other physiological parameters. Another problem not to be taken lightly is sweat collection. Indeed, sweat flow depends on many parameters such as gender, weather, obesity, physical exercises, medication [224].

To achieve a reliable detection, the sweat volume should be above 0.06 µL/mm^2 (*vs* electrode size) in terms of the biosensing measurement [225]. Sweat rate is expected to vary from 1 to 20 nL/min/gland. On the arm region, there are typically 150 glands/cm^2 [226]. In this case, sweat rate is estimated to be as high as 2 µL/min for the 5-mm-diameter sweat collection area. Physical exercises seem to be the easiest way to generate sweat flow forward the biosensor but this can only be performed punctuality or irregular because a real continuous glucose monitoring require at least six times measurement per day. This limited the use wearable glucose biosensors to people with daily physical activity (athletes), and make the use of such biosensors not adapted to peoples with health problems such as severe obesity, heart problems, or unfitness due to age (senior citizen), pregnancy, illness, or disability. For this reason, sweat generated in rest using low electrical current through thermal heating or chemical induction called iontophoresis has been proposed. However, their repeated application can be harmful to underlying skin and may be better suited for one-time use rather than continuous monitoring [227]. Recently, microfluidic based wearable biosensors have received particular attention, as they can precisely collect and deliver sweat to the defined bio sensing area [228]. These microfluidic wearable platforms contain microfluidic channels, reservoirs, and inlet/outlet ports, which work with capture and storage mechanisms. They enable direct capture of sweat from pores on the skin surface and transfer the sample to multiple sensors through different channels [229]. In summary wearable sweat glucose biosensors are still in their infancy and further investigations and development are required before these devices reach commercial stage and can really be used as glucose monitoring systems.

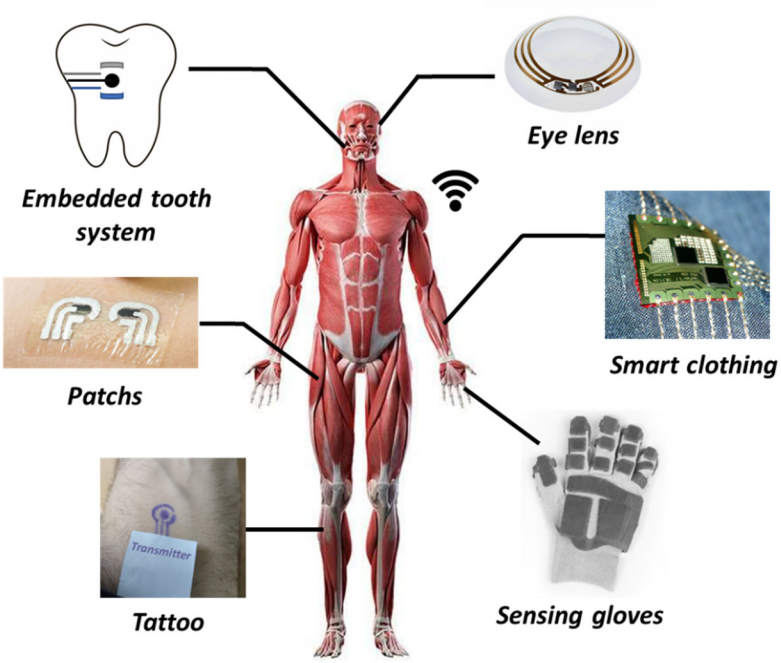

Figure 9. Wearable devices for non-invasive and real-time quantification in body fluids of biotargets (eye lens adapted from google, gloves adapted from PPS website: https://www.pressureprofile.com) [214, 230].

7. Artificial intelligence in glucose monitoring

Artificial intelligence (AI) including pattern analysis and classification algorithms with biosensors can bridge the gap between the data acquisition and analysis and achieve improved diagnostic and therapeutic accuracy [231]. Today, there is a real need for artificial intelligence that has become a trend in biosensing technology [216, 232–235]. Indeed, most of the commercial CGMs available now on the market can be connected to insulin pumps to automatize insulin delivery as closed-loop system. Thanks to the therapeutic artificial intelligence, including self-learning algorithm, it is possible to automate and personalize the treatment of diabetes. In other words, the CGM performs glucose measurement every 5 minutes approximately (depending on the manufacturer procedure), then, data are transmitted to a handset. AI analyzes the data in real time, while considering the patient's physiology, history and data entries (meals or exercise), it is possible to determine the correct dose of insulin to administer [236, 237]. This helps in optimizing and automatizing diabetes treatment while lowering the mental charge of the diabetes patients.

Many companies work today on the development of AI-powered algorithms for biomedical based-applications (e.g.: dynamic-biosensors, fullpower®, Diabeloop, ADVANCED ALGORITHMS 4 RADAR, etc.). They usually propose two types of products/services [238]: (1) algorithms hosted in a dedicated handset that usually integrate medical devices and help improving in personalizing treatment and, (2) a dedicated platform that store and automates data management as cloud-based systems. In addition, there is now real need to use biosensing platforms that integrate different biosensors to continuously monitor several physiological analytes at the same time. Due to this requirement, it is necessary to multiplex signals coming from different biosensors and correlate between their responses in real time. In such configuration, AI can help enabling quick and efficient data interpreting of a large complex dataset and help in the decision-making. Future works combining artificial intelligence and biosensing technologies are expected to lead to the next generation of smart, accurate, wearable, and wellness biosensors that especially allow increasing biosensors lifetime and improve patient's lifestyle [239–242].

On the other hand, AI can support the technology of biosensing development in a different way. Recently, Zebda and his co-authors have deposed a patent application to protect the invention of a method for determining an actual concentration of substrate using an array of self-calibrated biosensors. This method combined to AI should allow real-time correction of the deviation of biosensors responses using machine learning [243]. This needs a lot of experimental data generation to understand the behavior of each biosensor configuration in the mild conditions, enabling a new generation of glucose monitoring systems.

8. Conclusion

Continuous glucose monitoring systems were first introduced on the market more than 15 years ago and revolutionized the self-monitoring of blood glucose level. Such devices, in comparison to traditional fingerstick blood glucose meters, allow for continuous glucose level monitoring in near real time (1-15 min). However, one should bear in mind that the glucose level is measured from the interstitial fluid and the diffusion time must be taken into account to properly evaluate blood glucose level. Indisputable advantages of CGM are elimination/reduction of numerous finger pricks and almost immediate information about too high or too low glucose level, which decreases the risk of disease's complications (such as heart attack, stroke, kidney and nerve damage) as well as glycated Hb decrease with CGMs, suggesting decreased frequency and intensity of hyperglycemic events. Tracking glucose level over time can also provide information about body's response for various factors such as: meals or exercises and thus improve glycemic control. Moreover, CGMs are very helpful in case of children or in difficult measurement conditions for example during sleep, driving or pandemic. What is more, connection CGMs together with insulin pump open the possibility for the automated insulin distribution systems, which will act as an artificial pancreas. CGMs can be used for both professional (healthcare) and personal purposes. Additional benefits of CGM, which were confirmed in many clinical studies, include improvement in HbA1c level and reduction of glycemic variability. However, there are some restrictions in patient selection. Other limitations may be: delay between glucose level in interstitial fluid and in venous blood, costs and sensor durability. Future research trends are likely to bring to market more innovative devices displaying extended implantation time and/or noninvasive glucose measurements.

Acknowledgments

The authors would like to acknowledge the financial support from the Polish National Agency for Academic Exchange (PPN/BFR/2020/1/00052), CAMPUS FRANCE within the PARTENARIAT HUBERT CURIEN (PHC) Polonium grant 2021, Auvergne Rhone Alpes programs "Pack Amb Int'l 2019 and Pack Amb Int'l 2021" CNRS pre-maturation project 'BEPI" and Institut Carnot LSI (BIOEPC 2022 project).

Conflicts of Interest

The authors declare no conflict of interest.

Research Data Policy and Data Availability Statements

Not applicable.

References

1. International Diabetes Federation (2021) IDF Diabetes Atlas 10th edition.

2. Gregory GA, Robinson TIG, Linklater SE, et al (2022) Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol 10:741–760. https://doi.org/10.1016/S2213-8587(22)00218-2

3. Marcon LMR, Fanelli CG, Calafiore R (2022) Type 1 Diabetes (T1D) and Latent Autoimmune Diabetes in Adults (LADA): The Difference between a Honeymoon and a Holiday. Case Rep Endocrinol 9363543:1–5. https://doi.org/10.1155/2022/9363543

4. Erlich H, Valdes AM, Noble J, et al (2008) HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk analysis of the type 1 diabetes genetics consortium families. Diabetes 57:1084–1092. https://doi.org/10.2337/db07-1331

5. Yoo EH, Lee SY (2010) Glucose biosensors: An overview of use in clinical practice. Sensors 10:4558–4576

6. Davies MJ, D'Alessio DA, Fradkin J, et al (2018) Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 61:2461–2498. https://doi.org/10.1007/s00125-018-4729-5

7. Fralick M, Jenkins AJ, Khunti K, et al (2022) Global accessibility of therapeutics for diabetes mellitus. Nat Rev Endocrinol 18:199–204. https://doi.org/10.1038/s41574-021-00621-y

8. Reifsnider OS, Pimple P, Brand S, et al (2022) Cost-effectiveness of second-line empagliflozin versus liraglutide for type 2 diabetes in the United States. Diabetes Obes Metab 24:652–661. https://doi.org/10.1111/dom.14625

9. Yang W, Dall TM, Beronjia K, et al (2018) Economic costs of diabetes in the U.S. in 2017. Diabetes Care 41:917–928. https://doi.org/10.2337/dci18-0007

10. Walta AM, Keltanen T, Lindroos K, Sajantila A (2016) The usefulness of point-of-care (POC) tests in screening elevated glucose and ketone body levels postmortem. Forensic Sci Int 266:299–303. https://doi.org/10.1016/j.forsciint.2016.06.003

11. Lu M, Zuo Y, Guo J, et al (2018) Continuous glucose monitoring system can improve the quality of glucose control and glucose variability compared with point-of-care measurement in critically ill patients: A randomized controlled trial. Medicine (United States) 97:e12138. https://doi.org/10.1097/MD.0000000000012138

12. Montagnana M, Caputo M, Giavarina D, Lippi G (2009) Overview on self-monitoring of blood glucose. Clinica Chimica Acta 402:7–13. https://doi.org/10.1016/j.cca.2009.01.002

13. Pullano SA, Greco M, Bianco MG, et al (2022) Glucose biosensors in clinical practice: principles, limits and perspectives of currently used devices. Theranostics 12:493–511. https://doi.org/10.7150/thno.64035

14. Chehregosha H, Khamseh ME, Malek M, et al (2019) A View Beyond HbA1c: Role of Continuous Glucose Monitoring. Diabetes Therapy 10:853–863. https://doi.org/10.1007/s13300-019-0619-1

15. Piona C, Marigliano M, Mozzillo E, et al (2021) Relationships between HbA1c and continuous glucose monitoring metrics of glycaemic control and glucose variability in a large cohort of children and adolescents with type 1 diabetes. Diabetes Res Clin Pract 177:108933. https://doi.org/10.1016/j.diabres.2021.108933

16. Wang J (2008) Electrochemical glucose biosensors. Chem Rev 108:814–825

17. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, et al (2016) Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. The Lancet 388:2254–2263. https://doi.org/10.1016/S0140-6736(16)31535-5

18. Beck RW, Riddlesworth T, Ruedy K, et al (2017) Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections. JAMA 317:371. https://doi.org/10.1001/jama.2016.19975

19. Dunn TC, Xu Y, Hayter G, Ajjan RA (2018) Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: A European analysis of over 60 million glucose tests. Diabetes Res Clin Pract 137:37–46. https://doi.org/10.1016/j.diabres.2017.12.015

20. Benhamou PY, Franc S, Reznik Y, et al (2019) Closed-loop insulin delivery in adults with type 1 diabetes in real-life conditions: a 12-week multicentre, open-label randomised controlled crossover trial. Lancet Digit Health 1:e17–e25. https://doi.org/10.1016/S2589-7500(19)30003-2

21. Marling CR, Struble NW, Bunescu RC, et al (2013) A Consensus Perceived Glycemic Variability Metric. J Diabetes Sci Technol 7:871–879. https://doi.org/10.1177/193229681300700409

22. Bruen D, Delaney C, Florea L, Diamond D (2017) Glucose Sensing for Diabetes Monitoring: Recent Developments. Sensors 17:1866. https://doi.org/10.3390/s17081866

23. Sun M, Pei X, Xin T, et al (2022) A Flexible Microfluidic Chip-Based Universal Fully Integrated Nanoelectronic System with Point-of-Care Raw Sweat, Tears, or Saliva Glucose Monitoring for Potential Noninvasive Glucose Management. Anal Chem 94:1890–1900. https://doi.org/10.1021/acs.analchem.1c05174

24. Giaccari A, Morviducci L, Pastore L, et al (1998) Relative contribution of glycogenolysis and gluconeogenesis to hepatic glucose production in control and diabetic rats. A re-examination in the presence of euglycaemia. Diabetologia 41:307–314. https://doi.org/10.1007/s001250050908

25. Biazi GR, Frasson IG, Miksza DR, et al (2018) Decreased hepatic response to glucagon, adrenergic agonists, and cAMP in glycogenolysis, gluconeogenesis, and glycolysis in tumor-bearing rats. J Cell Biochem 119:7300–7309. https://doi.org/10.1002/jcb.27027

26. Wasserman DH (2008) Four grams of glucose. Am J Physiol Endocrinol Metab 295:11–21. https://doi.org/10.1152/ajpendo.90563.2008.-Four

27. Fuke Y, Fujita T, Satomura A, et al (2010) Alterations of Insulin Resistance and the Serum Adiponectin Level in Patients with Type 2 Diabetes Mellitus Under the Usual Antihypertensive Dosage of Telmisartan Treatment. Diabetes Technol Ther 12:393–398. https://doi.org/10.1089/dia.2009.0126?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub

28. Biazi GR, Frasson IG, Miksza DR, et al (2018) Decreased hepatic response to glucagon, adrenergic agonists, and cAMP in glycogenolysis, gluconeogenesis, and glycolysis in tumor-bearing rats. J Cell Biochem 119:7300–7309. https://doi.org/10.1002/jcb.27027

29. Scott SN, Anderson L, Morton JP, et al (2019) Carbohydrate Restriction in Type 1 Diabetes: A Realistic Therapy for Improved Glycaemic Control and Athletic Performance? Nutrients 11:1022. https://doi.org/10.3390/nu11051022

30. RAIVIO K, LAZAR C, KRUMHOLZ H, BECKER M (1981) The phosphogluconate pathway and synthesis of 5-phosphoribosyl-1-pyrophosphate in human fibroblasts. Biochimica et Biophysica Acta (BBA) - General Subjects 678:51–57. https://doi.org/10.1016/0304-4165(81)90046-5

31. Trogden KP, Lee J, Bracey KM, et al (2021) Microtubules regulate pancreatic β-cell heterogeneity via spatiotemporal control of insulin secretion hot spots. Elife 10:. https://doi.org/10.7554/eLife.59912

32. Rains JL, Jain SK (2011) Oxidative stress, insulin signaling, and diabetes. Free Radic Biol Med 50:567–575. https://doi.org/10.1016/j.freeradbiomed.2010.12.006

33. Kreft M, Jorgačevski J, Vardjan N, Zorec R (2016) Unproductive exocytosis. J Neurochem 137:880–889. https://doi.org/10.1111/jnc.13561

34. Lautenschläger J, Kaminski CF, Kaminski Schierle GS (2017) α-Synuclein – Regulator of Exocytosis, Endocytosis, or Both? Trends Cell Biol 27:468–479. https://doi.org/10.1016/j.tcb.2017.02.002

35. Mears D (2004) Regulation of Insulin Secretion in Islets of Langerhans by Ca2+Channels. Journal of Membrane Biology 200:57–66. https://doi.org/10.1007/s00232-004-0692-9

36. Hofmann C, Goldfine ID, Whittaker J (1989) The Metabolic and Mitogenic Effects of Both Insulin and Insulin-like Growth Factor Are Enhanced by Transfection of Insulin Receptors into NIH3T3 Fibroblasts. Journal of Biological Chemistry 264:8606–8611. https://doi.org/10.1016/S0021-9258(18)81835-X

37. Persaud SJ, Asare-Anane H, Jones PM (2002) Insulin receptor activation inhibits insulin secretion from human islets of Langerhans. FEBS Lett 510:225–228. https://doi.org/10.1016/S0014-5793(01)03268-9

38. Saltiel AR, Kahn CR (2001) Insulin signalling and the regulation of glucose and lipid metabolism. Nature 414:799–806. https://doi.org/10.1038/414799a

39. Bertolio R, Napoletano F, Mano M, et al (2019) Sterol regulatory element binding protein 1 couples mechanical cues and lipid metabolism. Nat Commun 10:. https://doi.org/10.1038/s41467-019-09152-7

40. Eeckhoute J, Formstecher P, Laine B (2004) Hepatocyte nuclear factor 4α enhances the hepatocyte nuclear factor 1α-mediated activation of transcription. Nucleic Acids Res 32:2586–2593. https://doi.org/10.1093/nar/gkh581

41. Jackson BC, Carpenter C, Nebert DW, Vasiliou V (2010) Update of human and mouse forkhead box (FOX) gene families. Hum Genomics 4:345. https://doi.org/10.1186/1479-7364-4-5-345

42. Tiraby C, Langin D (2005) PGC-1α, un co-activateur transcriptionnel impliqué dans le métabolisme. médecine/sciences 21:49–54. https://doi.org/10.1051/medsci/200521149

43. Erlich H, Valdes AM, Noble J, et al (2008) HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk analysis of the type 1 diabetes genetics consortium families. Diabetes 57:1084–1092. https://doi.org/10.2337/db07-1331

44. Roglic G, Norris SL (2018) Medicines for Treatment Intensification in Type 2 Diabetes and Type of Insulin in Type 1 and Type 2 Diabetes in Low-Resource Settings: Synopsis of the World Health Organization Guidelines on Second- and Third-Line Medicines and Type of Insulin for the Control of Blood Glucose Levels in Nonpregnant Adults With Diabetes Mellitus. Ann Intern Med 169:394. https://doi.org/10.7326/M18-1149

45. Ramondetti F, Sacco S, Comelli M, et al (2012) Type 1 diabetes and measles, mumps and rubella childhood infections within the Italian Insulin-dependent Diabetes Registry. Diabetic Medicine 29:761–766. https://doi.org/10.1111/j.1464-5491.2011.03529.x

46. Korkmaz HA, Ermiş Ç (2019) A case of immune-mediated type 1 diabetes mellitus due to congenital rubella infection. Ann Pediatr Endocrinol Metab 24:68–70. https://doi.org/10.6065/apem.2019.24.1.68

47. Ikegami H, Babaya N, Noso S (2021) β-Cell failure in diabetes: Common susceptibility and mechanisms shared between type 1 and type 2 diabetes. J Diabetes Investig 12:1526–1539. https://doi.org/10.1111/jdi.13576

48. Oguz A, Sahin M, Tuzun D, et al (2021) Irisin is a predictor of sarcopenic obesity in type 2 diabetes mellitus: A cross-sectional study. Medicine 100:e26529. https://doi.org/10.1097/MD.0000000000026529

49. Simonson DC, Hu B, Arterburn DE, et al (2022) Alliance of Randomized Trials of Medicine vs Metabolic Surgery in Type 2 Diabetes (ARMMS-T2D): Study rationale, design, and methods. Diabetes Obes Metab 24:1206–1215. https://doi.org/10.1111/dom.14680

50. Liu Z, Zhang Y, Graham S, et al (2020) Causal relationships between NAFLD, T2D and obesity have implications for disease subphenotyping. J Hepatol 73:263–276. https://doi.org/10.1016/j.jhep.2020.03.006

51. Razzak RA, Alshaiji AF, Qareeballa AA, et al (2018) High-normal blood glucose levels may be associated with decreased spatial perception in young healthy adults. PLoS One 13:. https://doi.org/10.1371/journal.pone.0199051

52. Yang G, Li C, Gong Y, et al (2016) Assessment of insulin resistance in subjects with normal glucose tolerance, hyperinsulinemia with normal blood glucose tolerance, impaired glucose tolerance, and newly diagnosed type 2 diabetes (prediabetes insulin resistance research). J Diabetes Res 2016:. https://doi.org/10.1155/2016/9270768

53. Jara AJ, Zamora MA, Skarmeta AFG (2011) An Internet of things-based personal device for diabetes therapy management in ambient assisted living (AAL). Pers Ubiquitous Comput 15:431–440. https://doi.org/10.1007/s00779-010-0353-1

54. Maruthur NM, Tseng E, Hutfless S, et al (2016) Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes. Ann Intern Med 164:740. https://doi.org/10.7326/M15-2650

55. Blüher M (2014) Adipokines – removing road blocks to obesity and diabetes therapy. Mol Metab 3:230–240. https://doi.org/10.1016/j.molmet.2014.01.005

56. Muda R, Sawicki P, Ginszt M (2021) Perceived food palatability, blood glucose level and future discounting: Lack of evidence for blood glucose level's impact on reward discounting. PLoS One 16:. https://doi.org/10.1371/journal.pone.0255484

57. Husdal R, Thors Adolfsson E, Leksell J, Nordgren L (2021) Diabetes care provided by national standards can improve patients' self-management skills: A qualitative study of how people with type 2 diabetes perceive primary diabetes care. Health Expectations 24:1000–1008. https://doi.org/10.1111/hex.13247

58. Walta AM, Keltanen T, Lindroos K, Sajantila A (2016) The usefulness of point-of-care (POC) tests in screening elevated glucose and ketone body levels postmortem. Forensic Sci Int 266:299–303. https://doi.org/10.1016/j.forsciint.2016.06.003

59. Heo YJ, Takeuchi S (2013) Towards Smart Tattoos: Implantable Biosensors for Continuous Glucose Monitoring. Adv Healthc Mater 2:43–56. https://doi.org/10.1002/adhm.201200167

60. Noakes TD (2022) What Is the Evidence That Dietary Macronutrient Composition Influences Exercise Performance? A Narrative Review. Nutrients 14:862. https://doi.org/10.3390/nu14040862

61. Storey HL, van Pelt MH, Bun S, et al (2018) Diagnostic accuracy of self-administered urine glucose test strips as a diabetes screening tool in a low-resource setting in Cambodia. BMJ Open 8:e019924. https://doi.org/10.1136/bmjopen-2017-019924

62. Dallosso HM, Bodicoat DH, Campbell M, et al (2015) Self-monitoring of blood glucose versus self-monitoring of urine glucose in adults with newly diagnosed Type 2 diabetes receiving structured education: A cluster randomized controlled trial. Diabetic Medicine 32:414–422. https://doi.org/10.1111/dme.12598

63. Müller N, Kämmer K, Kloos C, et al (2015) Postprandial self-monitoring of urine glucose reflects glycaemic control in people with relatively well controlled Type 2 diabetes mellitus not treated with insulin: A retrospective cohort study. Diabetic Medicine 32:958–962. https://doi.org/10.1111/dme.12718

64. Aakre KM, Watine J, Bunting PS, et al (2012) Self-monitoring of blood glucose in patients with diabetes who do not use insulin-are guidelines evidence-based? Diabetic Medicine 29:1226–1236. https://doi.org/10.1111/j.1464-5491.2012.03659.x

65. Suh S, Kim JH (2015) Glycemic Variability: How Do We Measure It and Why Is It Important? Diabetes Metab J 39:273. https://doi.org/10.4093/dmj.2015.39.4.273

66. Kraaijeveld SR (2021) Continuous Glucose Monitoring as a Matter of Justice. HEC Forum 33:345–370. https://doi.org/10.1007/s10730-020-09413-9

67. Caduff A, Lutz HU, Heinemann L, et al (2011) Dynamics of blood electrolytes in repeated hyper-and/or hypoglycaemic events in patients with type 1 diabetes. Diabetologia 54:2678–2689. https://doi.org/10.1007/s00125-011-2210-9

68. Alfadhly A, Darraj H, Alamlki B, et al (2022) Hyperglycaemic and hypoglycaemic emergencies among patients with diabetes mellitus who participated in pilgrims of the 2019/1440H Hajj season. J Family Med Prim Care 11:312. https://doi.org/10.4103/jfmpc.jfmpc_1096_21

69. de la Paz E, Barfidokht A, Rios S, et al (2021) Extended Noninvasive Glucose Monitoring in the Interstitial Fluid Using an Epidermal Biosensing Patch. Anal Chem 93:12767–12775. https://doi.org/10.1021/acs.analchem.1c02887

70. Fried DA, Fried R (2020) Can Type 2 Diabetes Sufferers Actually Estimate Serum Glucose Level From Interstitial Fluid Glucose Level: A Diabetes Patient's Experience. J Patient Exp 7:307–310. https://doi.org/10.1177/2374373519847384

71. Voskanyan G, Keenan DB, Mastrototaro JJ, Steil GM (2007) Putative Delays in Interstitial Fluid (ISF) Glucose Kinetics Can Be Attributed to the Glucose Sensing Systems Used to Measure Them Rather than the Delay in ISF Glucose Itself. J Diabetes Sci Technol 1:639–644. https://doi.org/10.1177/193229680700100507

72. Cengiz E, Tamborlane W v. (2009) A Tale of Two Compartments: Interstitial Versus Blood Glucose Monitoring. Diabetes Technol Ther 11:S-11-S-16. https://doi.org/10.1089/dia.2009.0002

73. Keenan DB, Mastrototaro JJ, Voskanyan G, Steil GM (2009) Delays in Minimally Invasive Continuous Glucose Monitoring Devices: A Review of Current Technology. J Diabetes Sci Technol 3:1207–1214. https://doi.org/10.1177/193229680900300528

74. Ma K, Yuen JM, Shah NC, et al (2011) In vivo, transcutaneous glucose sensing using surface-enhanced spatially offset raman spectroscopy: Multiple rats, improved hypoglycemic accuracy, low incident power, and continuous monitoring for greater than 17 days. Anal Chem 83:9146–9152. https://doi.org/10.1021/ac202343e

75. Herman A, Aerts O, Baeck M, et al (2017) Allergic contact dermatitis caused by isobornyl acrylate in Freestyle® Libre, a newly introduced glucose sensor. Contact Dermatitis 77:367–373. https://doi.org/10.1111/cod.12866

76. Hong YJ, Lee H, Kim J, et al (2018) Multifunctional Wearable System that Integrates Sweat-Based Sensing and Vital-Sign Monitoring to Estimate Pre-/Post-Exercise Glucose Levels. Adv Funct Mater 28:. https://doi.org/10.1002/adfm.201805754

77. Lee H, Song C, Hong YS, et al (2017) Wearable/disposable sweat-based glucose monitoring device with multistage transdermal drug delivery module. Sci Adv 3:1601314. https://doi.org/10.1126/sciadv.1601314

78. Xiao G, He J, Chen X, et al (2019) A wearable, cotton thread/paper-based microfluidic device coupled with smartphone for sweat glucose sensing. Cellulose 26:4553–4562. https://doi.org/10.1007/s10570-019-02396-y

79. Liu X, Zhang W, Lin Z, et al (2021) Coupling of Silk Fibroin Nanofibrils Enzymatic Membrane with Ultra-Thin PtNPs/Graphene Film to Acquire Long and Stable On-Skin Sweat Glucose and Lactate Sensing. Small Methods 5:2000926. https://doi.org/10.1002/smtd.202000926

80. Karpova E v., Shcherbacheva E v., Galushin AA, et al (2019) Noninvasive diabetes monitoring through continuous analysis of sweat using flow-through glucose biosensor. Anal Chem 91:3778–3783. https://doi.org/10.1021/acs.analchem.8b05928

81. Bhide A, Muthukumar S, Prasad S (2018) CLASP (Continuous lifestyle awareness through sweat platform): A novel sensor for simultaneous detection of alcohol and glucose from

passive perspired sweat. Biosens Bioelectron 117:537–545. https://doi.org/10.1016/j.bios.2018.06.065

82. Munje RD, Muthukumar S, Prasad S (2017) Lancet-free and label-free diagnostics of glucose in sweat using Zinc Oxide based flexible bioelectronics. Sens Actuators B Chem 238:482–490. https://doi.org/10.1016/j.snb.2016.07.088

83. Bhide A, Muthukumar S, Saini A, Prasad S (2018) Simultaneous lancet-free monitoring of alcohol and glucose from low-volumes of perspired human sweat. Sci Rep 8:6507. https://doi.org/10.1038/s41598-018-24543-4

84. Eslami R, Azizi N, Ghaffarian SR, et al (2022) Highly sensitive and selective non-enzymatic measurement of glucose using arraying of two separate sweat sensors at physiological pH. Electrochim Acta 404:139749. https://doi.org/10.1016/j.electacta.2021.139749

85. Baca JT, Finegold DN, Asher SA (2007) Tear Glucose Analysis for the Noninvasive Detection and Monitoring of Diabetes Mellitus. Ocul Surf 5:280–293. https://doi.org/10.1016/S1542-0124(12)70094-0

86. Badugu R, Lakowicz JR, Geddes CD (2005) A glucose-sensing contact lens: from bench top to patient. Curr Opin Biotechnol 16:100–107. https://doi.org/10.1016/j.copbio.2004.12.007

87. Duong HD, Sohn O-J, Rhee J il (2020) Development of a Ratiometric Fluorescent Glucose Sensor Using an Oxygen-Sensing Membrane Immobilized with Glucose Oxidase for the Detection of Glucose in Tears. Biosensors (Basel) 10:86. https://doi.org/10.3390/bios10080086

88. Badugu R, Lakowicz JR, Geddes CD (2004) Noninvasive Continuous Monitoring of Physiological Glucose Using a Monosaccharide-Sensing Contact Lens. Anal Chem 76:610–618. https://doi.org/10.1021/ac0303721

89. Ruan J-L, Chen C, Shen J-H, et al (2017) A Gelated Colloidal Crystal Attached Lens for Noninvasive Continuous Monitoring of Tear Glucose. Polymers (Basel) 9:125. https://doi.org/10.3390/polym9040125

90. Lee W-C, Koh EH, Kim D-H, et al (2021) Plasmonic contact lens materials for glucose sensing in human tears. Sens Actuators B Chem 344:130297. https://doi.org/10.1016/j.snb.2021.130297

91. Hu Y, Jiang X, Zhang L, et al (2013) Construction of near-infrared photonic crystal glucose-sensing materials for ratiometric sensing of glucose in tears. Biosens Bioelectron 48:94–99. https://doi.org/10.1016/j.bios.2013.03.082

92. Cui Y, Zhang H, Zhu J, et al (2022) Correlations of Salivary and Blood Glucose Levels among Six Saliva Collection Methods. Int J Environ Res Public Health 19:4122. https://doi.org/10.3390/ijerph19074122

93. Jurysta C, Bulur N, Oguzhan B, et al (2009) Salivary Glucose Concentration and Excretion in Normal and Diabetic Subjects. J Biomed Biotechnol 2009:1–6. https://doi.org/10.1155/2009/430426

94. Zhang W, Du Y, Wang ML (2015) Noninvasive glucose monitoring using saliva nano-biosensor. Sens Biosensing Res 4:23–29. https://doi.org/10.1016/j.sbsr.2015.02.002

95. Arakawa T, Kuroki Y, Nitta H, et al (2016) Mouthguard biosensor with telemetry system for monitoring of saliva glucose: A novel cavitas sensor. Biosens Bioelectron 84:106–111. https://doi.org/10.1016/j.bios.2015.12.014

96. Zhang W, Du Y, Wang ML (2015) Noninvasive glucose monitoring using saliva nano-biosensor. Sens Biosensing Res 4:23–29. https://doi.org/10.1016/j.sbsr.2015.02.002

97. Chen J, Zhu X, Ju Y, et al (2019) Electrocatalytic oxidation of glucose on bronze for monitoring of saliva glucose using a smart toothbrush. Sens Actuators B Chem 285:56–61. https://doi.org/10.1016/j.snb.2019.01.017

98. Adeniyi O, Nwahara N, Mwanza D, et al (2021) Nanohybrid electrocatalyst based on cobalt phthalocyanine-carbon nanotube-reduced graphene oxide for ultrasensitive detection of glucose in human saliva. Sens Actuators B Chem 348:130723. https://doi.org/10.1016/j.snb.2021.130723

99. Machado A, Maneiras R, Bordalo AA, Mesquita RBR (2018) Monitoring glucose, calcium, and magnesium levels in saliva as a non-invasive analysis by sequential injection multi-parametric determination. Talanta 186:192–199. https://doi.org/10.1016/j.talanta.2018.04.055

100. Koushki E, Mirzaei Mohammadabadi F, Baedi J, Ghasedi A (2020) The effects of glucose and glucose oxidase on the Uv-vis spectrum of gold nanoparticles: A study on optical biosensor for saliva glucose monitoring. Photodiagnosis Photodyn Ther 30:101771. https://doi.org/10.1016/j.pdpdt.2020.101771

101. Bollella P, Gorton L, Ludwig R, Antiochia R (2017) A Third Generation Glucose Biosensor Based on Cellobiose Dehydrogenase Immobilized on a Glassy Carbon Electrode Decorated with Electrodeposited Gold Nanoparticles: Characterization and Application in Human Saliva. Sensors 17:1912. https://doi.org/10.3390/s17081912

102. Eggeling L, Bott M, Marienhagen J (2015) Novel screening methods—biosensors. Curr Opin Biotechnol 35:30–36. https://doi.org/10.1016/j.copbio.2014.12.021

103. Wang J, Katz E (2010) Digital biosensors with built-in logic for biomedical applications—biosensors based on a biocomputing concept. Anal Bioanal Chem 398:1591–1603. https://doi.org/10.1007/s00216-010-3746-0

104. Borisov SM, Wolfbeis OS (2008) Optical Biosensors. Chem Rev 108:423–461. https://doi.org/10.1021/cr068105t

105. Ramanathan K, Jönsson BR, Danielsson B (2001) Sol–gel based thermal biosensor for glucose. Anal Chim Acta 427:1–10. https://doi.org/10.1016/S0003-2670(00)01095-3

106. Ronkainen NJ, Halsall HB, Heineman WR (2010) Electrochemical biosensors. Chem Soc Rev 39:1747–1763. https://doi.org/10.1039/b714449k

107. Roman A, Janier-Dubry A, Hanicq C, et al (2007) Comparison of accuracy of glucose-oxidase-based and glucose-dehydrogenase-based point-of-care glucometers. Crit Care 11:P142. https://doi.org/10.1186/cc5302

108. Okuda-Shimazaki J, Yoshida H, Sode K (2020) FAD dependent glucose dehydrogenases – Discovery and engineering of representative glucose sensing enzymes -. Bioelectrochemistry 132:107414. https://doi.org/10.1016/j.bioelechem.2019.107414

109. Li T, Lee HB, Park K (1998) Comparative stereochemical analysis of glucose-binding proteins for rational design of glucose-specific agents. J Biomater Sci Polym Ed 9:327–344. https://doi.org/10.1080/09205063.1998.9753059

110. Si P, Huang Y, Wang T, Ma J (2013) Nanomaterials for electrochemical non-enzymatic glucose biosensors. RSC Adv 3:3487. https://doi.org/10.1039/c2ra22360k

111. Wei M, Qiao Y, Zhao H, et al (2020) Electrochemical non-enzymatic glucose sensors: recent progress and perspectives. Chemical Communications 56:14553–14569. https://doi.org/10.1039/d0cc05650b

112. Aslan K, Lakowicz JR, Geddes CD (2004) Nanogold-plasmon-resonance-based glucose sensing. Anal Biochem 330:145–155. https://doi.org/10.1016/j.ab.2004.03.032

113. Nguyen HH, Lee SH, Lee UJ, et al (2019) Immobilized Enzymes in Biosensor Applications. Materials 12:121. https://doi.org/10.3390/ma12010121

114. Chmayssem A, Hauchard D (2015) New detection method for alkylphenol traces in water based on an integrated electrochemical cell sensor. Revue des Sciences de l'Eau 28:35–40. https://doi.org/10.7202/1030005ar

115. Hernández-Cruz M, Galán-Vidal CA, Álvarez-Romero GA, et al (2017) Behavior of Two and Three Electrode Configuration and Different Mediators in Working Electrode on Development of Disposable Screen-Printing Biosensors for Determination of Free Cholesterol. J Mex Chem Soc 57:47–53. https://doi.org/10.29356/jmcs.v57i1.237

116. Mondal H, Mondal S (2020) Clarke Error Grid Analysis on Graph Paper and Microsoft Excel. J Diabetes Sci Technol 14:499. https://doi.org/10.1177/1932296819890875

117. Sengupta S, Handoo A, Haq I, et al (2022) Clarke Error Grid Analysis for Performance Evaluation of Glucometers in a Tertiary Care Referral Hospital. Indian Journal of Clinical Biochemistry 37:199–205. https://doi.org/10.1007/s12291-021-00971-4

118. Wang H-C, Lee A-R (2015) Recent developments in blood glucose sensors. J Food Drug Anal 23:191–200. https://doi.org/10.1016/j.jfda.2014.12.001

119. Hassan MH, Vyas C, Grieve B, Bartolo P (2021) Recent Advances in Enzymatic and Non-Enzymatic Electrochemical Glucose Sensing. Sensors 21:4672. https://doi.org/10.3390/s21144672

120. Soranzo T, ben Tahar A, Chmayssem A, et al (2022) Electrochemical Biosensing of Glucose Based on the Enzymatic Reduction of Glucose. Sensors 22:7105. https://doi.org/10.3390/s22197105

121. Tang Z, Louie RF, Lee JH, et al (2001) Oxygen effects on glucose meter measurements with glucose dehydrogenase- and oxidase-based test strips for point-of-care testing. Crit Care Med 29:1062–1070. https://doi.org/10.1097/00003246-200105000-00038

122. Karyakin AA, Gitelmacher O v., Karyakina EE (1995) Prussian Blue-Based First-Generation Biosensor. A Sensitive Amperometric Electrode for Glucose. Anal Chem 67:2419–2423. https://doi.org/10.1021/ac00110a016

123. Chmayssem A, Verplanck N, Tanase CE, et al (2021) Development of a multiparametric (bio)sensing platform for continuous monitoring of stress metabolites. Talanta 229:122275. https://doi.org/10.1016/j.talanta.2021.122275

124. Chmayssem A, Petit L, Verplanck N, et al (2022) Characterization of the Impact of Classical Cell-culture Media on the Response of Electrochemical Sensors. Electroanalysis 34:1201–1211. https://doi.org/10.1002/elan.202100534

125. Chmayssem A, Tanase CE, Verplanck N, et al (2022) New Microfluidic System for Electrochemical Impedance Spectroscopy Assessment of Cell Culture Performance: Design and Development of New Electrode Material. Biosensors (Basel) 12:452. https://doi.org/10.3390/bios12070452

126. Luiz de Mattos I (2001) Evaluation of glucose biosensors based on Prussian Blue and lyophilised, crystalline and cross-linked glucose oxidases (CLEC®). Talanta 54:963–974. https://doi.org/10.1016/S0039-9140(01)00367-8

127. Garjonyte R, Malinauskas A (2000) Amperometric glucose biosensors based on Prussian Blue–and polyaniline–glucose oxidase modified electrodes. Biosens Bioelectron 15:445–451. https://doi.org/10.1016/S0956-5663(00)00101-9

128. Che X, Yuan R, Chai Y, et al (2010) Amperometric glucose biosensor based on Prussian blue-multiwall carbon nanotubes composite and hollow PtCo nanochains. Electrochim Acta 55:5420–5427. https://doi.org/10.1016/j.electacta.2010.04.091

129. Ledo A, Fernandes E, Brett CMA, Barbosa RM (2020) Enhanced selectivity and stability of ruthenium purple-modified carbon fiber microelectrodes for detection of hydrogen peroxide in brain tissue. Sens Actuators B Chem 311:127899. https://doi.org/10.1016/j.snb.2020.127899

130. Tian F, Llaudet E, Dale N (2007) Ruthenium purple-mediated microelectrode biosensors based on sol-gel film. Anal Chem 79:6760–6766. https://doi.org/10.1021/ac070822f

131. Tian F, Llaudet E, Dale N (2007) Ruthenium purple-mediated microelectrode biosensors based on sol-gel film. Anal Chem 79:6760–6766. https://doi.org/10.1021/ac070822f

132. Milton RD, Hickey DP, Abdellaoui S, et al (2015) Rational design of quinones for high power density biofuel cells. Chem Sci 6:4867–4875. https://doi.org/10.1039/c5sc01538c

133. Scheller FW, Schubert F, Neumann B, et al (1991) Second generation biosensors. Biosens Bioelectron 6:245–253. https://doi.org/10.1016/0956-5663(91)80010-U

134. Seiwert B, Karst U (2008) Ferrocene-based derivatization in analytical chemistry. Anal Bioanal Chem 390:181–200. https://doi.org/10.1007/s00216-007-1639-7

135. Laurinavicius V, Kurtinaitiene B, Liauksminas V, et al (1999) Oxygen insensitive glucose biosensor based on PQQ-dependent glucose dehydrogenase. Anal Lett 32:299–316. https://doi.org/10.1080/00032719908542822

136. Seiwert B, Karst U (2008) Ferrocene-based derivatization in analytical chemistry. Anal Bioanal Chem 390:181–200. https://doi.org/10.1007/s00216-007-1639-7

137. Kausaite-Minkstimiene A, Mazeiko V, Ramanaviciene A, et al (2014) Evaluation of Some Redox Mediators in the Design of Reagentless Amperometric Glucose Biosensor. Electroanalysis 26:1528–1535. https://doi.org/10.1002/elan.201400023

138. Silveira CM, Almeida MG (2013) Small electron-transfer proteins as mediators in enzymatic electrochemical biosensors. Anal Bioanal Chem 405:3619–3635. https://doi.org/10.1007/s00216-013-6786-4

139. Pijanowska DG, Kossakowska A, Torbicz W (2011) Electroconductive Polymers in (Bio)chemical Sensors. Biocybern Biomed Eng 31:43–57. https://doi.org/10.1016/S0208-5216(11)70025-0

140. Di J, Peng S, Shen C, et al (2007) One-step method embedding superoxide dismutase and gold nanoparticles in silica sol-gel network in the presence of cysteine for construction of third-generation biosensor. Biosens Bioelectron 23:88–94. https://doi.org/10.1016/j.bios.2007.03.011

141. Palmisano F, Zambonin PG, Centonze D, Quinto M (2002) A disposable, reagentless, third-generation glucose biosensor based on overoxidized poly(pyrrole)/tetrathiafulvalene - Tetracyanoquinodimethane composite. Anal Chem 74:5913–5918. https://doi.org/10.1021/ac0258608

142. Xu S, Qin X, Zhang X, Zhang C (2015) A third-generation biosensor for hydrogen peroxide based on the immobilization of horseradish peroxidase on a disposable carbon nanotubes modified screen–printed electrode. Microchimica Acta 182:1241–1246. https://doi.org/10.1007/s00604-014-1444-x

143. Wadkins RM, Golden JP, Ligler FS (1995) Calibration of Biosensor Response Using Simultaneous Evanescent Wave Excitation of Cyanine-Labeled Capture Antibodies and Antigens. Anal Biochem 232:73–78. https://doi.org/10.1006/abio.1995.9958

144. Li H, Dauphin-Ducharme P, Ortega G, Plaxco KW (2017) Calibration-Free Electrochemical Biosensors Supporting Accurate Molecular Measurements Directly in Undiluted Whole Blood. J Am Chem Soc 139:11207–11213. https://doi.org/10.1021/jacs.7b05412

145. Chaichi MJ, Ehsani M (2016) A novel glucose sensor based on immobilization of glucose oxidase on the chitosan-coated Fe3O4 nanoparticles and the luminol-H2O2-gold nanoparticle chemiluminescence detection system. Sens Actuators B Chem 223:713–722. https://doi.org/10.1016/j.snb.2015.09.125

146. Kang X, Mai Z, Zou X, et al (2007) A novel glucose biosensor based on immobilization of glucose oxidase in chitosan on a glassy carbon electrode modified with gold-platinum alloy nanoparticles/multiwall carbon nanotubes. Anal Biochem 369:71–79. https://doi.org/10.1016/j.ab.2007.07.005

147. Donmez S, Arslan F, Sarı N, et al (2017) Glucose biosensor based on immobilization of glucose oxidase on a carbon paste electrode modified with microsphere-attached l-glycine. Biotechnol Appl Biochem 64:745–753. https://doi.org/10.1002/bab.1533

148. Kondratowicz I, Shalayel I, Nadolska M, et al (2022) Impact of Lactic Acid and Genipin Concentration on Physicochemical and Mechanical Properties of Chitosan Membranes. J Polym Environ. https://doi.org/10.1007/s10924-022-02691-z

149. Rauf S, Ihsan A, Akhtar K, et al (2006) Glucose oxidase immobilization on a novel cellulose acetate- polymethylmethacrylate membrane. J Biotechnol 121:351–360. https://doi.org/10.1016/j.jbiotec.2005.08.019

150. Coulet PR, Gautheron DC (1981) Enzymes immobilized on collagen membranes: A tool for fundamental research and enzyme engineering. J Chromatogr A 215:65–72. https://doi.org/10.1016/S0021-9673(00)81386-2

151. Hina A, Saadeh W (2022) Noninvasive Blood Glucose Monitoring Systems Using Near-Infrared Technology—A Review. Sensors 22:4855. https://doi.org/10.3390/s22134855

152. Zubkovs V, Wang H, Schuergers N, et al (2022) Bioengineering a glucose oxidase nanosensor for near-infrared continuous glucose monitoring. Nanoscale Adv 4:2420–2427. https://doi.org/10.1039/D2NA00092J

153. Newman JD, Turner APF (2005) Home blood glucose biosensors: A commercial perspective. Biosens Bioelectron 20:2435–2453. https://doi.org/10.1016/j.bios.2004.11.012

154. Wang X, Zhang A, Zhi M, et al (2010) Glucose concentration measured by the hybrid coherent anti-Stokes Raman-scattering technique. Phys Rev A (Coll Park) 81:013813. https://doi.org/10.1103/PhysRevA.81.013813

155. Yuan H, Ji W, Chu S, et al (2018) Fiber-optic surface plasmon resonance glucose sensor enhanced with phenylboronic acid modified Au nanoparticles. Biosens Bioelectron 117:637–643. https://doi.org/10.1016/j.bios.2018.06.042

156. Odaci D, Gacal BN, Gacal B, et al (2009) Fluorescence sensing of glucose using glucose oxidase modified by PVA-pyrene prepared via “click” chemistry. Biomacromolecules 10:2928–2934. https://doi.org/10.1021/bm900755y

157. Li H, Liu C, Wang D, Zhang C (2017) Chemiluminescence cloth-based glucose test sensors (CCGTSs): A new class of chemiluminescence glucose sensors. Biosens Bioelectron 91:268–275. https://doi.org/10.1016/j.bios.2016.12.004

158. Mao X, Lu Y, Zhang X, Huang Y (2018) β-Cyclodextrin functionalization of metal-organic framework MOF-235 with excellent chemiluminescence activity for sensitive glucose biosensing. Talanta 188:161–167. https://doi.org/10.1016/j.talanta.2018.05.077

159. Yu M, Zhao K, Zhu X, et al (2017) Development of near-infrared ratiometric fluorescent probe based on cationic conjugated polymer and CdTe/CdS QDs for label-free determination of glucose in human body fluids. Biosens Bioelectron 95:41–47. https://doi.org/10.1016/j.bios.2017.03.065

160. Pickup JC, Hussain F, Evans ND, et al (2005) Fluorescence-based glucose sensors. Biosens Bioelectron 20:2555–2565. https://doi.org/10.1016/j.bios.2004.10.002

161. van Enter BJ, von Hauff E (2018) Challenges and perspectives in continuous glucose monitoring. Chemical Communications 54:5032–5045. https://doi.org/10.1039/c8cc01678j

162. Klonoff DC (2012) Overview of Fluorescence Glucose Sensing: A Technology with a Bright Future. J Diabetes Sci Technol 6:1242–1250. https://doi.org/10.1177/193229681200600602

163. Li W, Luo W, Li M, et al (2021) The Impact of Recent Developments in Electrochemical POC Sensor for Blood Sugar Care. Front Chem 9:723186. https://doi.org/10.3389/fchem.2021.723186

164. Teymourian H, Barfidokht A, Wang J (2020) Electrochemical glucose sensors in diabetes management: An updated review (2010-2020). Chem Soc Rev 49:7671–7709. https://doi.org/10.1039/d0cs00304b

165. Hovorka R (2006) Continuous glucose monitoring and closed-loop systems. Diabetic Medicine 23:1–12. https://doi.org/10.1111/j.1464-5491.2005.01672.x

166. Rodbard D (2017) Continuous glucose monitoring: A review of recent studies demonstrating improved glycemic outcomes. Diabetes Technol Ther 19:S25–S37. https://doi.org/10.1089/dia.2017.0035

167. Mortellaro M, DeHennis A (2014) Performance characterization of an abiotic and fluorescent-based continuous glucose monitoring system in patients with type 1 diabetes. Biosens Bioelectron 61:227–231. https://doi.org/10.1016/j.bios.2014.05.022

168. Franc S, Benhamou PY, Borot S, et al (2021) No more hypoglycaemia on days with physical activity and unrestricted diet when using a closed-loop system for 12 weeks: A post hoc secondary analysis of the multicentre, randomized controlled Diabeloop WP7 trial. Diabetes Obes Metab 23:2170–2176. https://doi.org/10.1111/dom.14442

169. Knoll C, Peacock S, Wäldchen M, et al (2022) Real-world evidence on clinical outcomes of people with type 1 diabetes using open-source and commercial automated insulin dosing systems: A systematic review. Diabetic Medicine 39:. https://doi.org/10.1111/dme.14741

170. Amadou C, Franc S, Huneker E, et al (2022) Short course corticosteroid treatment and closed-loop insulin delivery system: The experience of the DBLG1 pre-launch. Diabetes Metab 48:101294. https://doi.org/10.1016/j.diabet.2021.101294

171. Longo R, Sperling S (2019) Personal versus professional continuous glucose monitoring: When to use which on whom. Diabetes Spectrum 32:183–193. https://doi.org/10.2337/ds18-0093

172. Moser O, Pandis M, Aberer F, et al (2019) A head-to-head comparison of personal and professional continuous glucose monitoring systems in people with type 1 diabetes: Hypoglycaemia remains the weak spot. Diabetes Obes Metab 21:1043–1048. https://doi.org/10.1111/dom.13598

173. Klonoff DC, Ahn D, Drincic A (2017) Continuous glucose monitoring: A review of the technology and clinical use. Diabetes Res Clin Pract 133:178–192. https://doi.org/10.1016/j.diabres.2017.08.005

174. Carlson AL, Mullen DM, Bergenstal RM (2017) Clinical Use of Continuous Glucose Monitoring in Adults with Type 2 Diabetes. Diabetes Technol Ther 19:S-4-S-11. https://doi.org/10.1089/dia.2017.0024

175. Takeishi S, Inoue T (2021) Comparison Between Glycemic Variability Values Calculated From Professional-CGM and Glycemic Variability Values Calculated From Personal-CGM. J Endocr Soc 5:A330–A330. https://doi.org/10.1210/jendso/bvab048.674

176. Yoo JH, Kim JH (2020) Time in Range from Continuous Glucose Monitoring: A Novel Metric for Glycemic Control. Diabetes Metab J 44:828–839. https://doi.org/10.4093/dmj.2020.0257

177. Blumer I (2016) The Contemporary Role of Masked Continuous Glucose Monitoring in a Real-Time World. J Diabetes Sci Technol 10:790–792. https://doi.org/10.1177/1932296815619182

178. Fantasia KL, Stockman M-C, Ju Z, et al (2021) Professional continuous glucose monitoring and endocrinology eConsult for adults with type 2 diabetes in primary care: Results of a clinical pilot program. J Clin Transl Endocrinol 24:100254. https://doi.org/10.1016/j.jcte.2021.100254

179. Liebl A, Henrichs HR, Heinemann L, et al (2013) Continuous Glucose Monitoring: Evidence and Consensus Statement for Clinical Use. J Diabetes Sci Technol 7:500–519. https://doi.org/10.1177/193229681300700227

180. Rivera-Ávila DA, Esquivel-Lu AI, Salazar-Lozano CR, et al (2021) The effects of professional continuous glucose monitoring as an adjuvant educational tool for improving glycemic control in patients with type 2 diabetes. BMC Endocr Disord 21:79. https://doi.org/10.1186/s12902-021-00742-5

181. Raviteja K v., Kumar R, Dayal D, Sachdeva N (2019) Clinical efficacy of Professional Continuous Glucose Monitoring in improving glycemic control among children with Type 1 Diabetes Mellitus: An Open-label Randomized Control Trial. Sci Rep 9:6120. https://doi.org/10.1038/s41598-019-42555-6

182. American Diabetes Association Professional Practice Committee (2022) Diabetes Technology: Standards of Medical Care in Diabetes — 2022. Diabetes Care 45:S97–S112. https://doi.org/10.2337/dc22-S007

183. Grunberger G, Sherr J, Allende M, et al (2021) American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons With Diabetes Mellitus. Endocrine Practice 27:505–537. https://doi.org/10.1016/j.eprac.2021.04.008

184. Borot S, Benhamou PY, Atlan C, et al (2018) Practical implementation, education and interpretation guidelines for continuous glucose monitoring: A French position statement. Diabetes Metab 44:61–72. https://doi.org/10.1016/j.diabet.2017.10.009

185. Akturk HK, Dowd R, Shankar K, Derdzinski M (2021) Real-World Evidence and Glycemic Improvement Using Dexcom G6 Features. Diabetes Technol Ther 23:S-21-S-26. https://doi.org/10.1089/dia.2020.0654

186. Matuleviciene V, Joseph J, Andelin M, et al (2014) A clinical trial of the accuracy and treatment experience of the Dexcom G4 Sensor (Dexcom G4 System) and enlite sensor (Guardian REAL-Time System) tested simultaneously in ambulatory patients with type 1 diabetes. Diabetes Technol Ther 16:759–767. https://doi.org/10.1089/dia.2014.0238

187. Welsh JB, Gao P, Derdzinski M, et al (2019) Accuracy, utilization, and effectiveness comparisons of different continuous glucose monitoring systems. Diabetes Technol Ther 21:128–132. https://doi.org/10.1089/dia.2018.0374

188. Kosiborod M, Gottlieb RK, Sekella JA, et al (2014) Performance of the Medtronic Sentrino continuous glucose management (CGM) system in the cardiac intensive care unit. BMJ Open Diabetes Res Care 2:e000037. https://doi.org/10.1136/bmjdrc-2014-000037

189. Calhoun P, Lum J, Beck RW, Kollman C (2013) Performance Comparison of the Medtronic Sof-Sensor and Enlite Glucose Sensors in Inpatient Studies of Individuals with Type 1 Diabetes. Diabetes Technol Ther 15:758–761. https://doi.org/10.1089/dia.2013.0042

190. Perrier L (2019) Accessing continuous glucose monitoring (CGM) Sensors in France and the US: A comparative case study of abbott's freestyle libre (FSL) System. J Commer Biotechnol 25:24–39. https://doi.org/10.5912/JCB873

191. Kropff J, Choudhary P, Neupane S, et al (2017) Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE study: A 180-day, prospective, multicenter, pivotal trial. Diabetes Care 40:63–68. https://doi.org/10.2337/dc16-1525

192. Christiansen MP, Klaff LJ, Brazg R, et al (2018) A Prospective Multicenter Evaluation of the Accuracy of a Novel Implanted Continuous Glucose Sensor: PRECISE II. Diabetes Technol Ther 20:197–206. https://doi.org/10.1089/dia.2017.0142

193. Domingo-Lopez DA, Lattanzi G, H. J. Schreiber L, et al (2022) Medical devices, smart drug delivery, wearables and technology for the treatment of Diabetes Mellitus. Adv Drug Deliv Rev 185:114280. https://doi.org/10.1016/j.addr.2022.114280

194. Heinemann L, Schoemaker M, Schmelzeisen-Redecker G, et al (2020) Benefits and Limitations of MARD as a Performance Parameter for Continuous Glucose Monitoring in the Interstitial Space. J Diabetes Sci Technol 14:135–150. https://doi.org/10.1177/1932296819855670

195. Reiterer F, Polterauer P, Schoemaker M, et al (2017) Significance and Reliability of MARD for the Accuracy of CGM Systems. J Diabetes Sci Technol 11:59–67. https://doi.org/10.1177/1932296816662047

196. Garg SK, Kipnes M, Castorino K, et al (2022) Accuracy and Safety of Dexcom G7 Continuous Glucose Monitoring in Adults with Diabetes. Diabetes Technol Ther 24:373–380. https://doi.org/10.1089/dia.2022.0011

197. Collyns OJ, Meier RA, Betts ZL, et al (2021) Improved Glycemic Outcomes With Medtronic MiniMed Advanced Hybrid Closed-Loop Delivery: Results From a Randomized Crossover Trial Comparing Automated Insulin Delivery With Predictive Low Glucose Suspend in People With Type 1 Diabetes. Diabetes Care 44:969–975. https://doi.org/10.2337/dc20-2250

198. Carlson AL, Sherr JL, Shulman DI, et al (2022) Safety and Glycemic Outcomes During the MiniMed™ Advanced Hybrid Closed-Loop System Pivotal Trial in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther 24:178–189. https://doi.org/10.1089/dia.2021.0319

199. Li Y, Cao B, Chen Q, et al (2022) Application of the FreeStyle® Libre Glucose Monitoring System in type 1 diabetes mellitus patients aged 1–4 years. Pediatr Diabetes 23:604–610. https://doi.org/10.1111/pedi.13368

200. Oyagüez I, Gómez-Peralta F, Artola S, et al (2021) Cost Analysis of FreeStyle Libre® 2 System in Type 2 Diabetes Mellitus Population. Diabetes Therapy 12:2329–2342. https://doi.org/10.1007/s13300-021-01064-4

201. Freckmann G (2020) Basics and use of continuous glucose monitoring (CGM) in diabetes therapy. Journal of Laboratory Medicine 44:71–79. https://doi.org/10.1515/labmed-2019-0189

202. Lorenz C, Sandoval W, Mortellaro M (2018) Interference Assessment of Various Endogenous and Exogenous Substances on the Performance of the Eversense Long-Term Implantable Continuous Glucose Monitoring System. Diabetes Technol Ther 20:344–352. https://doi.org/10.1089/dia.2018.0028

203. Christiansen MP, Garg SK, Brazg R, et al (2017) Accuracy of a Fourth-Generation Subcutaneous Continuous Glucose Sensor. Diabetes Technol Ther 19:446–456. https://doi.org/10.1089/dia.2017.0087

204. Gildon BW (2018) InPen smart insulin pen system: Product review and user experience. Diabetes Spectrum 31:354–358. https://doi.org/10.2337/ds18-0011

205. Arrieta A, Battelino T, Scaramuzza AE, et al (2022) Comparison of MiniMed 780G system performance in users aged younger and older than 15 years: Evidence from 12 870 real-world users. Diabetes Obes Metab 24:1370–1379. https://doi.org/10.1111/dom.14714

206. Petrovski G, al Khalaf F, Campbell J, et al (2022) Glycemic outcomes of Advanced Hybrid Closed Loop system in children and adolescents with Type 1 Diabetes, previously treated with Multiple Daily Injections (MiniMed 780G system in T1D individuals, previously treated with MDI). BMC Endocr Disord 22:80. https://doi.org/10.1186/s12902-022-00996-7

207. Petrovski G, al Khalaf F, Campbell J, et al (2022) Successful transitioning children and adolescents with type 1 diabetes from multiple daily injections to advanced hybrid closed-loop system in 10 days: a prospective intervention study on MiniMed 780G system. Acta Diabetol 59:743–746. https://doi.org/10.1007/s00592-022-01851-w

208. Rayman G, Kröger J, Bolinder J (2018) Could FreeStyle Libre™ sensor glucose data support decisions for safe driving? Diabetic Medicine 35:491–494. https://doi.org/10.1111/dme.13515

209. Hoss U, Budiman ES (2017) Factory-Calibrated Continuous Glucose Sensors: The Science Behind the Technology. Diabetes Technol Ther 19:S-44-S-50. https://doi.org/10.1089/dia.2017.0025

210. Barnard KD, Kropff J, Choudhary P, et al (2018) Acceptability of Implantable Continuous Glucose Monitoring Sensor. J Diabetes Sci Technol 12:634–638. https://doi.org/10.1177/1932296817735123

211. Ma K, Yuen JM, Shah NC, et al (2011) In vivo, transcutaneous glucose sensing using surface-enhanced spatially offset raman spectroscopy: Multiple rats, improved hypoglycemic accuracy, low incident power, and continuous monitoring for greater than 17 days. Anal Chem 83:9146–9152. https://doi.org/10.1021/ac202343e

212. Ramadoss P, Rahman MI, Perumal A, et al (2020) Non-Invasive, Non-Enzymatic, Biodegradable and Flexible Sweat Glucose Sensor and Its Electrochemical Studies. ChemistrySelect 5:11305–11321. https://doi.org/10.1002/slct.202002622

213. Yao Y, Chen J, Guo Y, et al (2021) Integration of interstitial fluid extraction and glucose detection in one device for wearable non-invasive blood glucose sensors. Biosens Bioelectron 179:113078. https://doi.org/10.1016/j.bios.2021.113078

214. Kim J, Campbell AS, Wang J (2018) Wearable non-invasive epidermal glucose sensors: A review. Talanta 177:163–170. https://doi.org/10.1016/j.talanta.2017.08.077

215. Lerner MB, Kybert N, Mendoza R, et al (2013) Scalable, non-invasive glucose sensor based on boronic acid functionalized carbon nanotube transistors. Appl Phys Lett 102:183113. https://doi.org/10.1063/1.4804438

216. Aloraynan A, Rassel S, Xu C, Ban D (2022) Machine learning classifiers for noninvasive glucose detection using a single wavelength mid-infrared photoacoustic spectroscopy. Biomedical Spectroscopy, Microscopy, and Imaging II 121440I:45. https://doi.org/10.1117/12.2627014

217. Leelarathna L, Choudhary P, Wilmot EG, et al (2021) Hybrid closed-loop therapy: Where are we in 2021? Diabetes Obes Metab 23:655–660. https://doi.org/10.1111/dom.14273

218. Breton M, Farret A, Bruttomesso D, et al (2012) Fully Integrated Artificial Pancreas in Type 1 Diabetes. Diabetes 61:2230–2237. https://doi.org/10.2337/db11-1445

219. Boughton CK, Hovorka R (2019) Is an artificial pancreas (closed-loop system) for Type 1 diabetes effective? Diabetic Medicine 36:279–286. https://doi.org/10.1111/dme.13816

220. Park JB, Song MS, Ghosh R, et al (2021) Highly sensitive and flexible pressure sensors using position- and dimension-controlled ZnO nanotube arrays grown on graphene films. NPG Asia Mater 13:57. https://doi.org/10.1038/s41427-021-00324-w

221. Mohan AMV, Rajendran V, Mishra RK, Jayaraman M (2020) Recent advances and perspectives in sweat based wearable electrochemical sensors. TrAC Trends in Analytical Chemistry 131:116024. https://doi.org/10.1016/j.trac.2020.116024

222. Yeung KK, Huang T, Hua Y, et al (2021) Recent Advances in Electrochemical Sensors for Wearable Sweat Monitoring: A Review. IEEE Sens J 21:14522–14539. https://doi.org/10.1109/JSEN.2021.3074311

223. Kim J, Campbell AS, de Ávila BE-F, Wang J (2019) Wearable biosensors for healthcare monitoring. Nat Biotechnol 37:389–406. https://doi.org/10.1038/s41587-019-0045-y

224. Baker LB, Wolfe AS (2020) Physiological mechanisms determining eccrine sweat composition. Eur J Appl Physiol 120:719–752. https://doi.org/10.1007/s00421-020-04323-7

225. Guk K, Han G, Lim J, et al (2019) Evolution of Wearable Devices with Real-Time Disease Monitoring for Personalized Healthcare. Nanomaterials 9:813. https://doi.org/10.3390/nano9060813

226. Christodouleas DC, Kaur B, Chorti P (2018) From Point-of-Care Testing to eHealth Diagnostic Devices (eDiagnostics). ACS Cent Sci 4:1600–1616. https://doi.org/10.1021/acscentsci.8b00625

227. Khor SM, Choi J, Won P, Ko SH (2022) Challenges and Strategies in Developing an Enzymatic Wearable Sweat Glucose Biosensor as a Practical Point-Of-Care Monitoring Tool for Type II Diabetes. Nanomaterials 12:221. https://doi.org/10.3390/nano12020221

228. Padash M, Enz C, Carrara S (2020) Microfluidics by Additive Manufacturing for Wearable Biosensors: A Review. Sensors 20:4236. https://doi.org/10.3390/s20154236

229. Yeo JC, Kenry, Lim CT (2016) Emergence of microfluidic wearable technologies. Lab Chip 16:4082–4090. https://doi.org/10.1039/C6LC00926C

230. Linz T, Kallmayer C, Aschenbrenner R, Reichl H (2005) Embroidering electrical interconnects with conductive yarn for the integration of flexible electronic modules into fabric. In: Ninth IEEE International Symposium on Wearable Computers (ISWC'05). IEEE, pp 86–89

231. Jin X, Liu C, Xu T, et al (2020) Artificial intelligence biosensors: Challenges and prospects. Biosens Bioelectron 165:112412. https://doi.org/10.1016/j.bios.2020.112412

232. Mejía-Salazar JR, Rodrigues Cruz K, Materón Vásques EM, Novais de Oliveira Jr. O (2020) Microfluidic Point-of-Care Devices: New Trends and Future Prospects for eHealth Diagnostics. Sensors 20:1951. https://doi.org/10.3390/s20071951

233. Gopinath SCB, Ismail ZH, Shapiai MI, Sobran NMM (2022) Biosensing human blood clotting factor by dual probes: Evaluation by deep long short-term memory networks in time series forecasting. Biotechnol Appl Biochem 69:930–938. https://doi.org/10.1002/bab.2164

234. Jiang M, Zheng S, Zhu Z (2022) What can AI-TENG do for Low Abundance Biosensing? Front Bioeng Biotechnol 10:899858. https://doi.org/10.3389/fbioe.2022.899858

235. Oliveira ON, Oliveira MCF (2021) Sensing and Biosensing in the World of Autonomous Machines and Intelligent Systems. Frontiers in Sensors 2:752754. https://doi.org/10.3389/fsens.2021.752754

236. Hanaire H, Franc S, Borot S, et al (2020) Efficacy of the Diabeloop closed-loop system to improve glycaemic control in patients with type 1 diabetes exposed to gastronomic dinners or to sustained physical exercise. Diabetes Obes Metab 22:324–334. https://doi.org/10.1111/dom.13898

237. Benhamou PY, Huneker E, Franc S, et al (2018) Customization of home closed-loop insulin delivery in adult patients with type 1 diabetes, assisted with structured remote monitoring: the pilot WP7 Diabeloop study. Acta Diabetol 55:549–556. https://doi.org/10.1007/s00592-018-1123-1

238. Dixon TA, Williams TC, Pretorius IS (2021) Sensing the future of bio-informational engineering. Nat Commun 12:388. https://doi.org/10.1038/s41467-020-20764-2

239. Tittl A, John-Herpin A, Leitis A, et al (2019) Metaoberflächen-basierte molekulare Biosensorik unterstützt von künstlicher Intelligenz. Angewandte Chemie 131:14952–14965. https://doi.org/10.1002/ange.201901443

240. Ma X, Ahadian S, Liu S, et al (2021) Smart Contact Lenses for Biosensing Applications. Advanced Intelligent Systems 3:2000263. https://doi.org/10.1002/aisy.202000263

241. Liao X, Song W, Zhang X, et al (2020) A bioinspired analogous nerve towards artificial intelligence. Nat Commun 11:268. https://doi.org/10.1038/s41467-019-14214-x

242. Zhang J, Huang H, Song G, et al (2022) Intelligent biosensing strategies for rapid detection in food safety: A review. Biosens Bioelectron 202:114003. https://doi.org/10.1016/j.bios.2022.114003

243. Abdelkader Zebda, Philippe Cinquin, Don Martin (2021) Patent application: Method for determining an actual concentration of substrate using an array of self-calibrated biosensors and device for implementing the method. Ref. WO 2021/250627 A1. (1-40)