# Wearable Electrochemical Biosensors for Glucose Monitoring


**Marjan Majdinasab**

## 1 Introduction

Diabetes, also known as diabetes mellitus, is the most common metabolic disease related to carbohydrate metabolism. It is a group of endocrine disorders resulting from insulin deficiency and characterized by hyperglycemia or sustained high blood sugar (glucose) levels as a common effect of uncontrolled diabetes. Blood glucose concentrations in diabetic patients are higher than the normal range of 80–120 mg/dL (4.4–6.6 mM) [1]. Diabetes mellitus is one of the main causes of mortality and disability worldwide and a main health problem for most developed societies. According to the World Health Organization (WHO) report the number of diabetic individuals worldwide was approximately 171 million in 2000, and this is estimated to increase to 366 million by 2030 [2]. High levels of blood glucose lead to numerous complications such as higher risks of kidney failure, heart disease, stroke, blindness, and in some cases amputation [3]. Considering that there is no permanent treatment for diabetes, the only way to prevent these unwanted complications is disease management with routine blood glucose monitoring. Although laboratory tests are available for glucose monitoring in patients with diabetes but it requires frequent visits of patients to the laboratory, which is time-consuming and costly. To address this issue, self-monitoring of blood glucose has been established as a valuable tool for the management of diabetes. In order to be replaced by clinical tests, self-monitoring tools must meet some characteristics such as high accuracy and sensitivity, quick response, easy to use and low cost. This demand has been met by excessive research on glucose sensors using different transducer systems, i.e., electrochemical, acoustic, thermal, optical, and magnetic. Electrochemical biosensors specifically have been investigated extremely since the first generation of glucose sensors due to numerous

M. Majdinasab (✉)
Department of Food Science and Technology, School of Agriculture, Shiraz University, 71441-65186 Shiraz, Iran
e-mail: majdinasab@shirazu.ac.ir



K. Mitsubayashi (ed.), *Wearable Biosensing in Medicine and Healthcare*,
https://doi.org/10.1007/978-981-99-8122-9_3

advantages such as high accuracy and reproducibility, better sensitivity, simplicity, and low cost [2, 3]. Enzymes are the most common recognition element not only in electrochemical sensors but also in other types of glucose sensors due to their high selectivity towards glucose substrate. Enzymatic amperometric glucose biosensors, inspired by the first glucose biosensor developed by Clark and Lyons in 1962, are the most popular devices commercially available, and have been extensively studied in the last few decades. Currently, relying on the numerous researches conducted in the field of enzymatic electrochemical glucose biosensors, finger glucometers are commercially available as the common diagnostic standard tools for self-monitoring of blood glucose. Despite many advantages of finger glucometers, they are painful and invasive and also they don't have the ability to continuously monitor glucose [4]. Therefore, the efforts to improve glucose biosensors are still ongoing. Different approaches have been investigated in the performance of glucose enzyme electrodes. Moreover, one of the most interesting topics in recent years is the effort to develop wearable non-invasive or minimally invasive glucose monitoring devices, which have attracted the attention of many researchers in the field of biosensors. Wearable devices are able to receive physiological information worn on the human body by measuring dynamically changing contents of biomarkers in biofluids including interstitial fluid (ISF), sweat, saliva, and tears, while analyzing and storing the collected data by smart transmission and information processing systems [5, 6]. Among different kinds of glucose monitoring devices developed so far, wearable non-invasive and minimally invasive glucose sensors are of interest for diabetes management due to their ability to continuously monitor glucose levels. These devices are generally based on different techniques including optical, colorimetric, ultrasound, and electrochemical approaches [4]. Each of these techniques has its own pros and cons. However, wearable electrochemical sensors are exclusively attractive due to their noticeable advantages such as high selectivity and sensitivity, inherent miniaturization, low cost, high speed, low power requirements, and highly scalable fabrication by the use of screen-printing technology. Figure 1 shows the wide field of glucose detection approaches and distinguishes three different groups including invasive, minimally invasive, and non-invasive techniques. In invasive methods, there is direct detection of glucose in the blood like the technology used in glucose self-monitoring devices (finger glucometer). Minimally invasive methods are those that require extracting some body fluids (i.e., ISF, tears, saliva and sweat), with a single insertion into the skin and minimal pain, to measure the glucose concentration using an enzymatic reaction. In non-invasive techniques, biological fluids containing glucose at concentrations that are proportional to its concentration in the blood are collected without puncturing the skin [7].

One of the most effective wearable glucose monitoring systems that has recently been successfully implemented in several commercial platforms is wearable minimally invasive systems developed for continuous glucose monitoring. One of the most appealing wearable minimally invasive systems developed in recent years is microneedle-based systems to monitor glucose levels in the ISF using enzymatic reactions [8]. Although due to their small size, they have been considered to be minimally invasive, but in some cases, they can be associated with challenges such as tissue

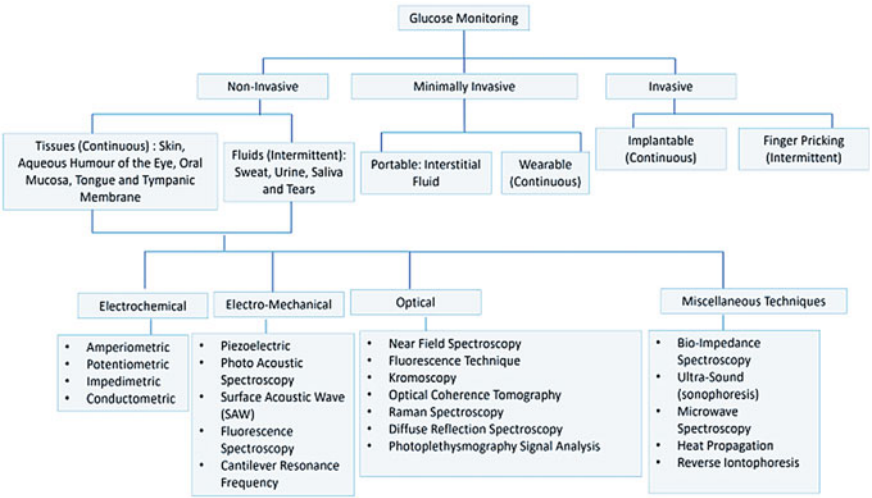



**Fig. 1** A review of various techniques for glucose measurement. Reprinted from Ref. [7] with permission

damage and microbial infection. Therefore, the development of fully non-invasive devices for continuous monitoring of glucose is the main goal of new generation of wearable biosensors. These new generation of biosensors should be non-invasive and able to measure glucose levels on a daily basis. Moreover, the results of glucose measurement can be transmitted wirelessly to the patient's physician.

The main goal of this chapter is to evaluate the history and current status of electrochemical glucose biosensors focusing on wearable electrochemical biosensors that are a growing trend of recent publications. Two types of wearable electrochemical glucose biosensors including microneedle-based sensors as minimally invasive devices, and flexible electrodes as non-invasive devices are evaluated. Principles of operation and various materials applied in these two groups of wearable electrochemical glucose biosensors with their advantages and limitations are discussed. Moreover, the advantages of self-powered wearable devices are explained.

## 2 Electrochemical Glucose Biosensors

The principle of electrochemistry-based transducers is the electron flow generated by a chemical reaction. Regarding electrochemical detection of glucose, this process mainly relies on oxidation/reduction reactions. During these reactions, glucose is converted to gluconic acid (gluconate). Electrochemical glucose biosensors are classified into two groups including enzymatic and non-enzymatic. In enzymatic biosensors, glucose oxidation can occur in the presence of enzyme while, in non-enzymatic

group glucose detection is based on activities of metal-centered electrocatalysts [3, 9, 10].

## 2.1 Enzymatic Electrochemical Glucose Biosensors

Since the first glucose biosensor proposed by Clark and Lyons, enzymatic glucose sensing has been employed ever since with more popularity and high potential such that the principle of detection in numerous glucose biosensors as well as commercial glucometers is enzymatic reactions. Enzymatic glucose biosensor of Clark and Lyons was fabricated by a thin layer of glucose oxidase (GOx) entrapped over an oxygen electrode through a semipermeable dialysis membrane [1]. In this system, monitoring of the oxygen consumption by the enzymatic reaction was an indicator for glucose detection.

In addition to GOx, two other kinds of enzymes including hexokinase and glucose-l-dehydrogenase (GDH) are used for glucose measurement. While the hexokinase method is used as the reference method in many clinical laboratories for accurate estimation of glucose in serum or plasma, GDH and GOx are two common enzymes employed in glucose biosensors and self-monitoring of blood glucose [11]. GDH and GOx differ in some features including selectivity towards glucose, cofactors, Michaelis constants ($K_m$), redox potential, cosubstrates, and turnover rate [12]. GOx is more common and considered as gold standard enzyme for glucose sensing due to its unique characteristics such as higher selectivity for glucose, relatively low cost, and good stability towards environmental conditions including high temperature, pH and ionic strength [2, 13]. Glucose detection using this enzyme relies on the following three reactions:

(1) $\text{Glucose} + \text{GOx–FAD}^+ \rightarrow \text{Gluconic acid} + \text{GOx–FADH}_2$
(2) $\text{GOx–FADH}_2 + \text{O}_2 \rightarrow \text{GOx–FAD} + \text{H}_2\text{O}_2$
(3) $\text{H}_2\text{O}_2 \rightarrow 2\text{H}^+ + \text{O}_2 + 2\text{e}$

Since GOx requires a redox cofactor for the catalysis of glucose oxidation, flavin adenine dinucleotide (FAD) plays this specific role as the initial electron acceptor. Therefore, in the first step, FAD is strongly bound to GOx. Then, GOx-FAD catalyzes the oxidation of β-D-glucose to gluconic acid. The produced $FADH_2$ is regenerated by reacting with molecular oxygen, resulting in the formation of hydrogen peroxides. On the other hand, $H_2O_2$ is oxidized at a catalytic, classically platinum anode. The electrode quickly detects the number of electron transfers, and the electron current corresponds to the number of glucose molecules in the blood [2, 12].

Three common strategies are employed for electrochemical detection of glucose including (1) measurement of glucose utilization; (2) measurement of the concentration of produced hydrogen peroxide; or (3) application of a permeable or immobilized mediator to transport electrons from the GOx to the electrode.

Despite a lot of advantages of GOx, this enzyme uses oxygen as an external electron acceptor in the oxidation reaction, thus device efficiency is sensitive to and

variable depending on the atmospheric oxygen level [14]. To overcome this limitation and increase sensing reliability, GDH does not require oxygen and is being employed in different types of glucose sensors. Recently, GDH-based biosensors relying on amperometric detection are increasing. GDHs are subdivided based on their redox cofactors; The GDHs utilizing the cofactor nicotine adenine dinucleotide (NAD) or nicotine adenine dinucleotide phosphate (NADP), GDHs utilizing the pyrroloquinoline quinone (PQQ) cofactor and FAD-dependent GDHs [15]. PQQ-GDH catalyzes not only the oxidation of glucose, but also of other sugars. Among these three members of GDHs family, FAD-GDH represents high thermal stability and substrate selectivity and does not require further cofactors or active catalysts. However, FAD-GDH shows ineffective electron transfer with the commercial $Ru(NH_3)_6$ mediator that is employed with GOx, and thus $Ru(dmo\text{-}bpy)_2Cl_2$ has been evaluated to be an efficient redox mediator for electron transfer with FAD-GDH [16].

## 2.2 *Different Generations of Enzymatic Electrochemical Glucose Biosensors*

Three kinds of enzymatic glucose biosensors have been proposed and are classified as first, second, and third-generation. Briefly, the first and second generation types are based on amperometric detection by monitoring electrochemical oxidation of hydrogen peroxide or reduction of oxygen for first generation-based sensors, or electrochemical oxidation of reduced mediators in the second generation types [17]

First-generation glucose sensors are enzymatic devices based on oxidizing glucose using GOx as a specific bioreceptor [1]. They have relied on the utilization of natural oxygen co-substrate and the production and recognition of $H_2O_2$ (Fig. 2) [18]. Although detection of hydrogen peroxide is simple and miniaturization of such systems is easy, but measurement of $H_2O_2$ requires a relatively high reduction potential in which other endogenous reducing species (e.g., uric acid, ascorbic acids and some drugs) in body fluids are also electroactive and can interfere with glucose detection [19, 20]. Another challenge of this system is the limitation of oxygen solubility in body fluids, which can lead to errors during measurement and low reproducibility of the test [1]. To address these challenges, oxygen was replaced with a non-physiological electron acceptor in second generation of glucose biosensors. In this system, the chemical mediator was able to shuttle electrons from the redox center of the GOx to the electrode surface in order to decrease detection potential (Fig. 2) [21]. Different kinds of artificial mediators including ferricyanide, quinines, tetrathiafulvalene (TTF), ferrocene, tetracyanoquinodimethane (TCNQ), methylene blue, thionine and methyl viologen were investigated to increase sensor efficiency [22–24]. Among these, ferrocene showed all the desirable characteristics of a mediator and was applied in the first commercial mediator-based glucometers [25, 26]. Due to high toxicity of the mentioned mediators, the third-generation glucose biosensors without the use of any chemical mediator and based on direct transfer between the enzyme and

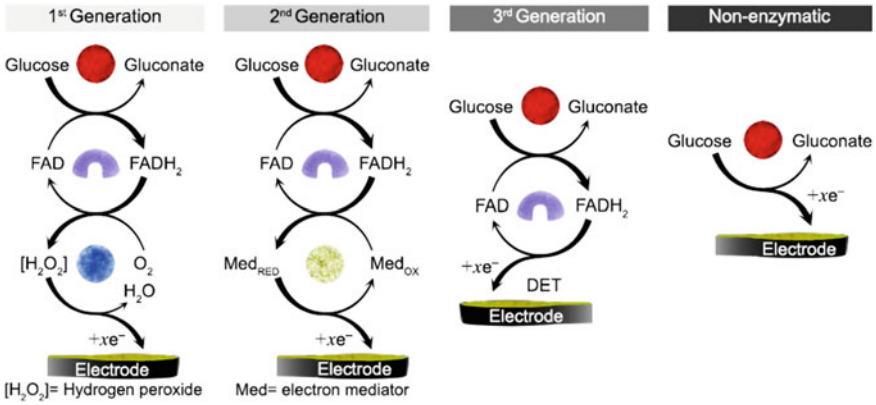



**Fig. 2** A schematic representation of different generations of electrochemical glucose biosensors. Reprinted from Ref. [40] with permission

electrode were developed (Fig. 2) [4, 20]. In these systems, the electrode can perform direct electron transfers using organic conducting materials based on charge-transfer complexes. Hence, the third-generation glucose sensors have resulted in implantable, needle-type systems for continuous in vivo monitoring of glucose. Conducting organic salts including tetrathiafulvalene-tetracyanoquinodimethane (TTF-TCNQ) are known as intermediates in the electrochemistry of GDH-PQQ enzymes as well as flavoproteins (GOx) [12]. Direct electron transfer in third-generation glucose sensors enhances electron transfer and provides a simple system for glucose monitoring [2].

## *2.3 Non-enzymatic Electrochemical Glucose Biosensors*

Despite many advantages of enzymatic glucose biosensors such as high specific catalytic action excellent selectivity and sensitivity, high efficiency and mild measurement conditions, they suffer from several limitations that arise from proteinaceous nature of enzymes [10, 27]. The performance of enzymatic group is highly dependent on environmental conditions including temperature, pH, humidity and toxic chemicals limiting their application [3, 10]. To address these challenges, non-enzymatic glucose sensors have been proposed based on the electrocatalytic oxidation of glucose, which can be detected optically or electrochemically (Fig. 2). Compared to optical sensors, non-enzymatic electrochemical sensors offer higher sensitivity, fast response, simpler operation, ease of miniaturization and scalability, lower cost, low power requirement, and portability [28]. Noble metals and their alloys (e.g., Pt, Au, Pd, and Rh) [29, 30], metal oxide (e.g., NiO and CuO) [31–33], and transition metals (e.g., Cu, Ni, Zn, and Mn) [34, 35], are mostly used materials in electrochemical glucose sensors due to their electrocatalytic activity. Moreover, they are mostly integrated with other nanostructures such as graphene [36], carbon nanotubes [37],

$MoS_2$ [38], and conducting polymers [39] to increase the sensitivity. Noble metals and their composites have been widely applied as the electrode materials for non-enzymatic glucose sensors due to their high electrocatalytic activity, better stability compared to enzymes and high sensitivity to the electro-oxidation of glucose [20].

Glucose oxidation through synthetic electrocatalysts is explained by two models including activated chemisorption model and incipient hydrous oxide adatom mediator (IHOAM) model. In activated chemisorption model oxidation process is initiated by the glucose adsorption onto catalyst (electrode) surface followed by breaking bonds and new intermediate formation. After glucose adsorption on the metal surface, it is oxidized to glucono-δ-lactone, which is further converted to gluconic acid. IHOAM model relies on reactive hydroxide species on the electrode surface generated during the electrocatalysis and their effect on many organic molecules' redox reactions [10]. Both models can be considered for catalytic reaction on noble metal electrodes, but they are not qualified to explain glucose oxidation on transition metals or metal oxides [3].

The main drawback of non-enzymatic glucose sensors is the absorption of glucose oxidation intermediates or solution active species which leads to blockage of electrode activity for direct glucose electro-oxidation. Moreover, non-enzymatic amperometric glucose sensors suffer from lower selectivity in comparison with enzymatic amperometric glucose biosensors due to the weakness of the electrocatalytic materials to specifically catalyze glucose oxidation [20].

## *2.4 Continuous Monitoring of Glucose Using Wearable Sensors*

Wearable sensing method is an emerging technology relying on a combination of chemistry, engineering, computer sciences, and wireless technology. This technology has made a considerable progress in the aspect of digital quantification of our daily health continuously. In this regard, continuous glucose monitoring (CGM) in different body fluids using wearable devices has gained considerable attention. CGM sensors are wearable non/minimally invasive tools that measure glucose concentration almost constantly (1–5 min sampling period) for multiple consecutive days/weeks reducing the need of the self-monitoring glucometers (Fig. 3a) and significantly increasing the information on blood glucose fluctuations [41]. In recent years, different mechanisms for non-invasive or at least minimally invasive CGM devices [42–45] have been investigated to meet all the basic needs of a sensor such as sensitivity, specificity, linearity within biological relevant range (Fig. 3b, c) [41]. Among different proposed techniques (i.e. optical, electrochemical, and piezoelectric), the one that is today used by most of the commercialized CGM devices is based on the concept of 1st or 2nd generation of electrochemical glucose biosensors relying on GOx reaction [1]. Commercial CGM device based on 3rd generation glucose sensors has been yet to be done.

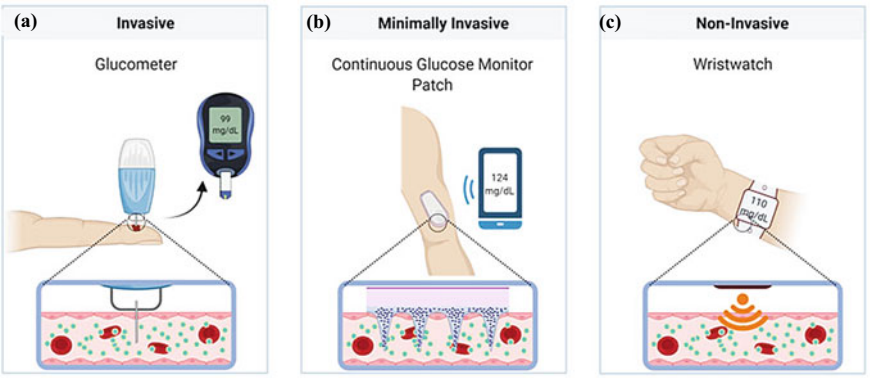



**Fig. 3** Different types of invasive, minimally invasive and non-invasive glucose monitoring devices. Reprinted from Ref. [49] with permission

The first prototype of wearable CGM sensor, Medtronic Minimed Gold, was introduced and approved by FDA in 1999 [46] and devices have evolved rapidly since then. The system was a wired-type glucose electrochemical needle-type sensor inserted in the subcutaneous tissue in the abdomen or on the arm, in a minimally invasive manner, and measured an electrical current signal produced by enzymatic reaction. The electrical signal is proportional to the glucose content in the interstitial fluid, which is then converted into a glucose concentration by a calibration method normally performed twice a day. Current Medtronic CGM devices are all equipped with wireless transmission. Dexcom Inc. launched their first CGM system in 2006, which also utilized 1st generation basis, and was equipped with wireless transmission. Abbott introduced the first 2nd generation type CGM device in 2008, by using their iconic technology redox-polymer hydrogel, that consisted osmium complex as electron mediator incorporated with GOx [17]. In recent years, many non-invasive (e.g., flexible electrodes) or minimally invasive (e.g., microneedles) electrochemical monitoring devices that perform glucose measurements in other biological fluids instead of blood have attracted the attention of research topics. It is worth noticing that although glucose is detectable in different body fluids such as sweat, saliva, urine, tears and ISF and thus glucose levels in these matrixes have the potential to correspond to blood glucose content [47] but, the glucose concentrations in these biofluids are much lower than those in blood, leading to large deviations in the measurement results from the actual blood glucose content. However, among the wearable devices, minimally invasive devices are preferred due to the use of ISF whose glucose concentration is closer to the blood plasma and has a reliable correlation with blood glucose levels.

Non-invasive CGM techniques have strict requirements for the environment and must overcome challenges such as those concerning noise interference, detection sensitivity, and stability. Most non-invasive sensing techniques are only employed for "proof of concept" and have not yet been used in clinicalapplications [48]. The most

extensively used CGM devices in clinical applications are currently based on minimally invasive electrochemical techniques. The minimally invasive electrochemical CGM sensors show several advantages of high sensitivity and stability, short response time, simple operation, and easy miniaturization. The features of these two categories of wearable CGM sensors are explained in more detail below.

### 2.4.1 Wearable Minimally Invasive CGM Systems

Primary CGM devices are blinded systems which record retrospective glucose data for professional use only. In these systems, a sensor probe ranging from 5 to 13 mm in length is implanted under the skin of a diabetic individual to continuously collect glucose data. A statistical report of the glucose concentrations is produced at the end of the wearing. A retrospective CGM sensor can represent the variations in a diabetic's glucose contents on several consecutive days and make a reference for physicians to investigate the diabetes treatment plan. The limitations are that the data processing is complicated and diabetics are not able to check their own glucose data in real-time. A real-time CGM sensor updates glucose information every 1 to 5 min [50]. Therefore, the glucose content and fluctuation graphs are created at any time, and the history of the results can also be reviewed. Moreover, the device is easy to wear and does not interfere with the normal daily life of diabetic person. Whenever the glucose concentration exceeds the threshold level set for hyperglycemia or hypoglycemia, the device will generate an alarm. Some products of Medtronic's Guardian™ Connect and Guardian™ Sensor 3 even are able to predict high or low glucose excursions up to 60 min in advance. The latest development in commercial CGM sensors is that the device is integrated with an insulin pump to create an artificial pancreas, so that insulin injection can be done automatically if necessary [48].

There are several critical technologies for the construction of minimally invasive electrochemical-based CGM systems. In this regard, several criteria should be considered to provide the best performance and minimal invasiveness and pain: (1) the size of implanted sensor probe should be small enough to minimize the incision zone and reduce implantation pain and the infection risk; (2) the enzyme activity should be preserved as much as possible to inhibit large enzyme losses during long-term operation, thereby increasing the sensitivity and stability of the sensor; (3) the sensor should be more biocompatible to reduce the effect of allogeneic reaction. In this regard, application of microneedles and biocompatible membranes and also immobilization of enzymes in sensor development can meet these requirements to a great extent.

#### Microneedle-Based Electrochemical CGM Systems

Microneedle-based CGM sensors have emerged in order to access ISF in an efficient, non-invasive and pain-free way and to reduce infection risk associated with

implantable probe. These systems are safer for patients by reducing the possibility of infections [51]. Due to the micron size (< 1 mm in length), they can penetrate the epidermis to reach the dermis without contacting the dermal neurons and blood vessels [52, 53]. Furthermore, microneedles possess a larger electrode surface area and show high sensitivity in both in vitro and in vivo tests. The type of microneedle and the materials applied for its fabrication play a main role in the design of microneedle-based biosensors to ensure full compatibility with both sensing elements integration and implementation for transdermal investigation [54]. Three main classes of materials including polymers, metals and silicon are generally used to fabricate microneedles. Polymers are usually used more than other materials due to their low cost and ease of construction. Different kinds of polymers such as epoxy-based negative photoresists [55, 56], acrylate-based polymers [57, 58] and polycarbonate [59, 60] have been investigated. In the case of electrochemical sensing, to increase electrical conductivity, polymeric microneedle is coated with metals, metal oxides, alloys (e.g., Au, Pt/IrOx, Ti/Au or Cr/Pt) or even conductive forms of carbon (e.g., carbon paste, carbon fibers or carbon nanotubes). Concerning metallic microneedles, the most popular materials include Pt, Au and W because of their superior conductivity and good biocompatibility. Silicon with the feature of excellent is extensively used to fabricate microneedles. Microneedles fabricated with hollow silicon can passively extract ISF by capillary action. Depending on the method of forming the materials, four different fabrication techniques can be used to develop microneedles. These techniques include lithography, micromachining, mold-filling, and computer assisted polymerization [54].

In microneedle-based electrochemical sensors for glucose monitoring, generally enzyme, in particular GOx, is used as a bioreceptor to modify microneedle electrodes for selective monitoring of glucose. For example, in several microneedle-based glucose sensors, poly(3,4-ethylenedioxythiophene) (PEDOT) was employed for the immobilization of GOx on the surface of platinum-coated stainless steel microneedle electrode. PEDOT also played the role of electrical mediator. On the other hand, Pt was applied due to high electrical conductivity and chemical stability. Therefore, with the combination of PEDOT, Pt and GOx, a highly sensitive and selective glucose sensor was obtained [61]. In another effort, Sharma et al. reported a minimally invasive glucose biosensor based on a microneedle array electrode fabricated from an epoxy-based negative photoresist (SU8 50) and developed for continuous measurement in the dermal compartment with minimal pain (Fig. 4a) [55]. The device was constructed by casting the structures in SU8 50, crosslinking and then metallizing with Pt or Ag to produce the working and reference electrodes, respectively. The metallized microneedle array electrodes were subsequently functionalized by entrapping GOx in electropolymerized polyphenol (PP) film. In vitro studies showed that the developed devise is able to measure glucose concentrations less than 0.5 mM with a response time of 15 s. After the microneedle insertion into the forearm of several volunteers for 24 h, no inflammation or skin irritation was reported by them.

Carbon-based nanomaterials are very interesting for the coverage of microneedles in order to increase electrical conductivity. In this regard, a microneedle-based

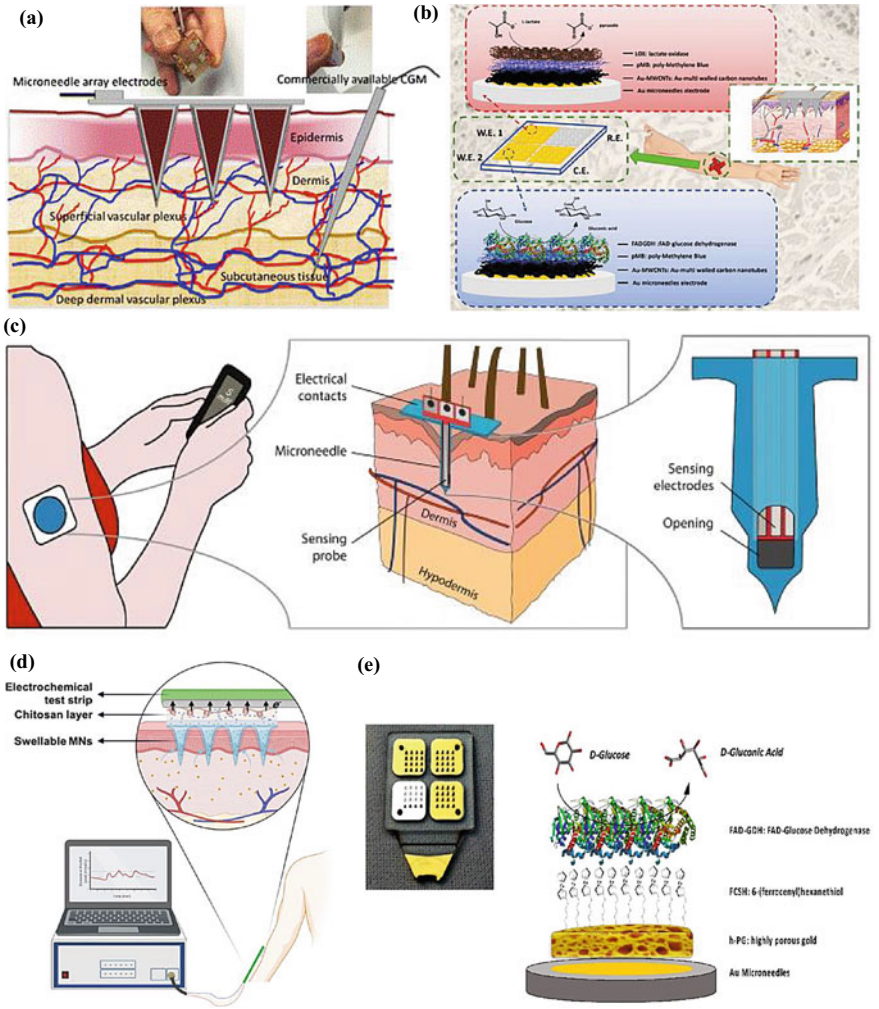



**Fig. 4** **a** Comparison of microneedle array electrodes and commercial CGM and the two areas of the skin cavity applied to reach the ISF. Reprinted from Ref. [55] with permission; **b** A microneedle-based biosensor array for the continuous and simultaneous detection of lactate and glucose in the artificial ISF. W.E.: working electrode; R.E.: reference electrode; C.E.: counter electrode. Ref [62]; **c** A CGM device based on hollow silicon microneedle. Reprinted from Ref. [65] with permission; **d** A CGM device combining swellable microneedles and electrochemical test strips for the evaluation of glucose or alcohol content in the skin's ISF. Reprinted from Ref. [68]; **e** A highly porous gold/6-(ferrocenyl)hexanethiol (FcSH)/FAD-GDH/Au microneedles-based biosensor for glucose monitoring in ISF. Reprinted from Ref. [59]

sensor array was fabricated for simultaneous monitoring of lactate and glucose in artificial ISF (Fig. 4b) [62]. The gold surface of the microneedles was modified by electrodeposition of multiwalled carbon nanotubes (MWCNTs) and subsequently by electropolymerization of methylene blue as the redox mediator to form second generation of glucose biosensor. Then, the modified microneedle was functionalized with lactate oxidase (LOX) in working electrode 1, and with the FAD-GDH in working electrode 2. The fabricated device showed a high sensitivity towards glucose and lactate.

In addition to glucose monitoring, microneedles can also act as ISF collector. In this regard, hollow microneedles, swelling microneedles and porous microneedles are able to collect ISF. In these kinds of microneedles, the sensing electrodes are integrated inside the microneedle. Therefore, microneedle not only can protect electrode from breakage or enzyme loss during insertion into the skin, but also it can collect glucose of ISF [48].

Hollow microneedles, manufactured using silicon, metals, or non-dissolving polymers, with empty space inside are a type of conventional transfusion needle [63]. They are widely used to collect ISF and blood. For sensing purpose, a rapid analysis system can be placed precisely on the outlet of hollow microneedle to distinguish analytes in collected biological fluids. Therefore, analyte (e.g., glucose) can be detected by hollow microneedle-based sensing device. However, the possibility of blocking the opening of the needle during the piercing of the skin is a major limitation for hollow MNs, which will result in resistance to flow. On the other hand, fabrication of hollow microneedles is significantly difficult, and those with high aspect ratios don't have the usual internal support structure for solid needles [64]. Ribet et al. (2018) fabricated a CGM device using hollow silicon microneedles (Fig. 4c). The device was based on the combination of an ultra-miniaturized electrochemical sensing probe inside of a single hollow microneedle, separately realized using standard silicon microfabrication procedures. The device relied only on passive capillary lumen filling without the need for complex fluid extraction mechanisms. Moreover, the transdermal portion of the system was fifty times smaller than that of commercial devices [65]. Since long-term stability and continuous monitoring remain unsolved challenges associated with electrochemical sensors, Parrilla et al. (2022) tried to overcome these challenges by developing a highly stable redox mediator bilayer for electrochemical sensing of glucose in ISF [66]. The biosensor was composed of screen-printed carbon electrodes (SPCE) modified with GOx and redox mediator bilayer of Prussian blue (PB)/nickel hexacyanoferrate (NiHCF) system to enhance the stability of the redox mediator layer. In addition, a diffusion-limited Nafion layer is applied to the electrode to increase the linearity of the biosensor to millimolar levels required for diabetes monitoring. After assessment of hollow MNs array for easy skin piercing, the biosensor was attached to the back of the hollow MNs array leaving a microfluidic cell. Finally, the hollow MNs sensor array was coupled to a syringe using microfluidic tubing. This design provided rapid ISF extraction and glucose analysis, as only the glucose diffusion into the SPCE results in long-term operation.

The swellable microneedles have obtained considerable attention due to swelling under the skin after absorption of ISF and also maintaining the structure without dissolving [67]. Swellable MNs are commonly constructed by physical crosslinking methods such as exposure to ultraviolet (UV) light with photoinitiators [63]. The major limitation of swellable microneedles is their lower mechanical strength. By selection of suitable polymers and fabrication method, a balance can be established between swelling and mechanical strength [67]. Zheng et al. (2022) developed a skin patch integrating swellable microneedles, made of swellable methacrylated hyaluronic acid, and electrochemical test strips for glucose and alcohol measurement in ISF [68]. This device was fabricated by adhering microneedle patch on the electrochemical strips using the chitosan as the connecting layer. The electrochemical strip was a screen-printed three-electrode strip which working electrode was first modified with a Prussian blue as mediator layer and subsequently functionalized with Gox. The microneedle penetrated the skin for extraction of ISF that flowed to the backing layer of microneedles and was analyzed by the test strip (Fig. 4d). In another example, Zheng et al. (2022) embedded wire electrodes in the tips of silk fibroin-microneedle and fabricated a swellable microneedle patch for in situ real-time detection of glucose in the ISF of skin or plant tissues [69]. Working and counter wire electrodes were made of platinum (Pt), while wire reference electrode was made of Ag/AgCl. Chitosan was used as the binder to immobilize GOx onto the surface of Pt wires. The wettable yet insoluble fibroin hydrogel provided good mechanical strength in dry conditions for easy tissue penetration. After insertion, fibroin MNs swelled and extracted biomarker-containing ISF into their polymeric matrix to reach the embedded electrodes. Rapid detection was achieved due to the immediate contact between the electrodes and the ISF. This microneedle strategy is suitable for long-term monitoring of glucose as well as other biomarkers.

Porous microneedles possess interconnected micro-sized pores throughout the entire structure of microneedle. They are usually fabricated from biocompatible metals, ceramics, or polymers with small randomly distributed and interconnected pores. Due to the continuous pores, the rapid absorption and collection of ISF can be reached through capillary action. Therefore, ISF extraction and the subsequent monitoring of glucose in fluids can be obtained using porous microneedles integrated with lab-on-chip biosensing devices. Increased fragility due to the large volume of holes is one of the disadvantages of porous microneedles [63]. Bollella et al. (2019) developed a highly porous gold microneedles-based second generation biosensor for minimally invasive monitoring of glucose in artificial ISF [59]. The highly porous microneedles-based electrode was fabricated using a simple electrochemical self-templating strategy that included two steps, gold electrodeposition and hydrogen bubbling at the electrode (Fig. 4e). The highly porous gold surface of the microneedles was modified by immobilization of 6-(ferrocenyl)hexanethiol as a redox mediator and then by immobilization of FAD-GDH enzyme using a drop-casting method. The device showed high sensitivity and stability. Porous metals have been investigated as highly active catalysts as well as sensitive electrodes due to their large surface area. Kai et al. (2021) developed porous microneedle electrodes (with a pore diameter of approximately 1 μm) by electroless plating of nickel and gold on the

porous polymer microneedles of poly(glycidyl methacrylate), and applied them to an enzymatic glucose sensor [70]. The GOx was immobilized on the gold-plated microneedle electrodes. The amperometry of glucose content in solution was determined using the fabricated electrode as the working electrode, together with the Ag/AgCl reference electrode and the gold counter electrode, both of which were made of microneedles. The porous structures of microneedle electrode resulted in increased sensitivity.

### 2.4.2 Wearable Non-invasive CGM Systems

As mentioned earlier, development of wearable non-invasive needle-free CGM devices provides a convenient tool to monitor the glucose concentration of diabetes patients without discomfortability and risk of infection. In recent years, a lot of wearable devices in different forms of watches, glasses and wrist/armbands have been developed for real-time and continuous monitoring of glucose level. However, current commercial devices are generally just miniaturized forms of conventional electronics that include rigid, bulky, and flat components. Such stiffness and bulkiness can not only disturb and annoy the devices, but also limit the matching contact of the devices with the human body [71]. Moreover, due to the need for advanced technologies and hardware combinations the production cost increases, which will be one of the major limitations of this kind of biosensors. To overcome these challenges and develop a fully wearable sensor system several important factors including the application of soft and flexible materials, wireless technologies, and high integrity should be considered. With recent advances in soft, stretchable, and flexible conducting materials, development of wearable biosensors has become easier. On the other hand, advances in wireless communication technologies and electronic engineering simplify data processing and transmission with a miniaturized electronic chip. The main advantage of wireless power transfer is that it just needs a simple antenna circuit, which provides a vast choice of materials and structures. Using tribo and piezoelectric mechanisms, energy harvesters enable charging of electricity through body movement, thus providing an easy way to charge regardless of environmental conditions [72, 73]. The combination of all functional ingredients with different functions, characteristics and shapes in small and compact devices should include rigorous methodological approaches.

Non-invasive and on-body analysis of glucose can be performed in different biofluids such as tear, saliva, sweat, and ISF.

Tears include various biomarkers such as electrolytes, metabolites (e.g., glucose, lactate, and ascorbate), and proteins (e.g., lysozyme, lactoferrin, lipocalin, and albumin). Tear biomarkers directly diffuse from blood, resulting in a close correlation between the biomarker level in tears and blood [74]. Moreover, accessibility of tear is very easy. However, sample collection of tears is challenging due to the small sample volume, rapid evaporation during sample preparation, eye irritation, and deficiency of tear fluids of individuals who suffer from dry eye syndrome. Wearable tear sensors consist of eyeglasses and contact lenses [74].

Saliva contains proteins, hormones and small metabolites such as glucose. A main advantage of saliva is the possibility of collecting a large volume of sample in a non-invasive, low cost and simple way. However, the concentration of biomarkers in saliva is generally lower than blood and other non-invasive biofluids. Moreover, due to presence of food particles, bacteria and other contaminants, some sample preparation steps such as filtering or centrifuging are required before analysis. One of saliva wearable sensors include electrodes well-equipped in mouthguard [74].

Sweat as an epidermally available biofluid contains electrolytes, metabolites (e.g., glucose), proteins, small molecules and disease biomarkers. Analysis of sweat has several limitations such as variation of sweat secretion (upon weather condition, physical activity, stress, and chemical stimulus), sweat rate, sample evaporation, and skin surface contamination. Tattoo biosensors including conductive inks attached on the wearable flexible materials are an example of electrochemical biosensors for the sweat analyzing [74].

ISF, an extracellular fluid surrounding tissue cells, contains proteins, electrolytes and metabolites. Concentration of analytes in ISF is similar to blood plasma leading to reliable correlation between ISF and blood plasma. However, ISF components should be excreted at the surface of skin by an additional approach such as reverse iontophoresis (RI) and sonophoresis for non-invasive sampling [75]. RI is the most widely used technique in electrochemical glucose sensing relying on ISF sample. This technique led to the development of the GlucoWatch® as a commercial wearable non-invasive electrochemical glucose monitoring device [76]. RI is a needle-free method for extracting biomolecules through intact skin to gain the goal of blood glucose detection. RI consists of two mechanisms: (1) electromigration, the direct interaction between charged ions and applied electric field, and (2) electroosmosis, a connective solvent flow from anode to cathode direction. For the charged compounds, electromigration is the major transport mechanism [77]. The total quantity of charge transferred depends on the strength and duration of the electric field. For the uncharged compounds (e.g., glucose), electroosmosis driven by voltage is the main extraction mechanism. The shape, size and position of electrodes are considered as important parameters for RI. Different shapes of electrodes such as thin disks (same as GlucoWatch) to snakes, ridges or otherwise have been used. It is not only necessary that the electrode can be closely connected to the human skin, but also keeping a suitable micro-distance from the skin surface. Therefore, flexible materials are generally used for the electrode fabrication [77].

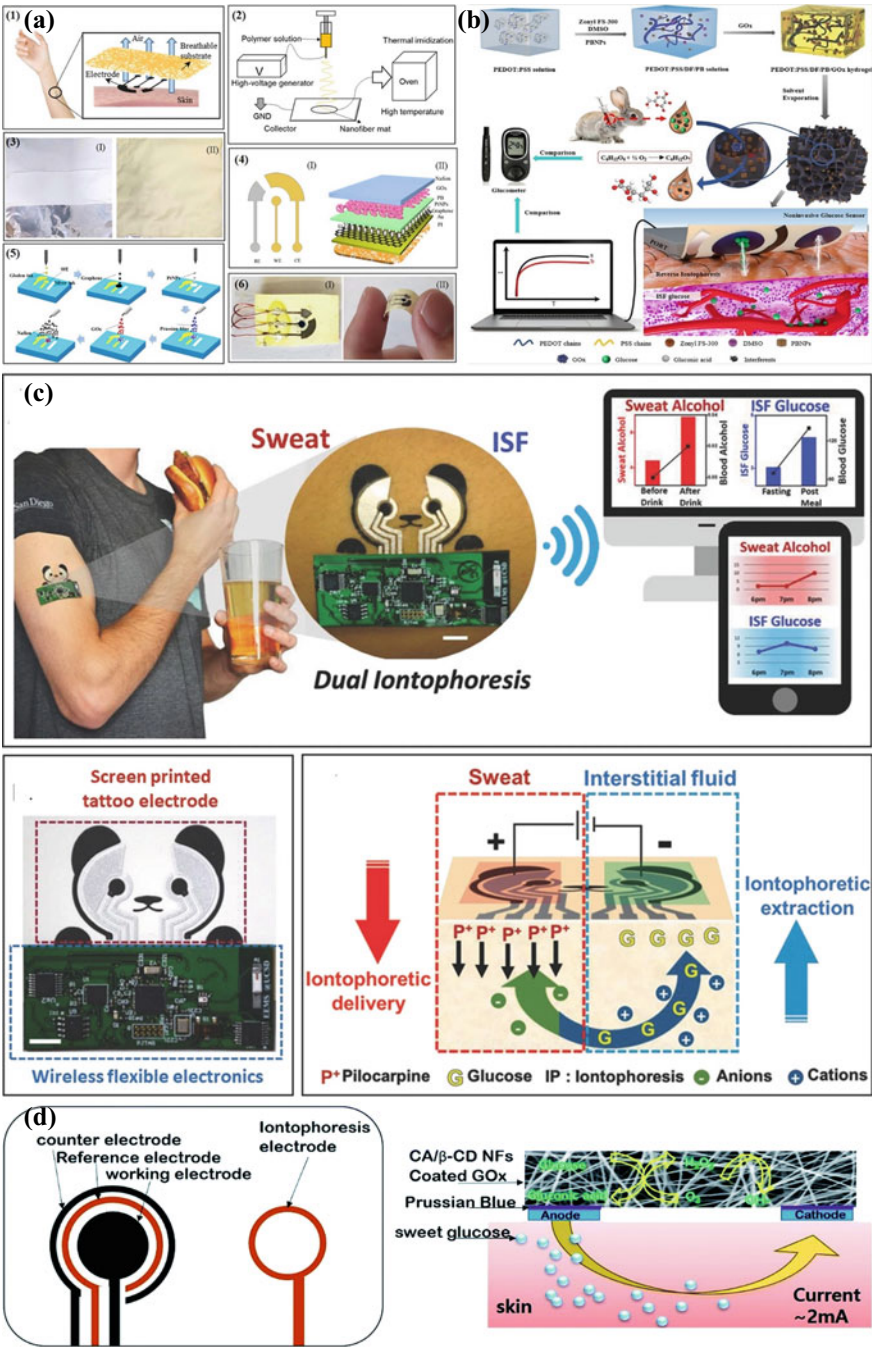
### Flexible Electrodes: Materials and Fabrication Methods

Selection of flexible materials with appropriate characteristics such as stretching, bending, high compression and tensile strength, and twisting is of particular importance in design of a wearable system. The most common flexible materials employed for wearable glucose biosensors include polyethylene terephthalate (PET) and polydimethylsiloxane (PDMS). The most important features of these materials are their transparency, wide commercial availability, and the ability to print with a wide range

of electrically conductive materials. In addition, fibrous materials including cellulose, polyurethane, polyamide, and cotton fibers, particularly moisture management as a kind of cotton material with 100% moisture absorption, are suggested as inexpensive, available and flexible materials in wearable electrochemical CGM devices. A flexible and wearable glucose biosensor was fabricated using hydrophobic PDMS and hydrophilic 2-methacryloyloxyethyl phosphorylcholine (MPC) copolymerized with dodecyl methacrylate (DMA) by photolithography and ion beam sputtering techniques [78]. Electrodes (Pt working electrode and Ag/AgCl reference/counter electrode) were formed on the PDMS using microelectromechanical (Soft-MEMS) techniques. Thus, a flexible hydrogen peroxide electrode was obtained. The gas-permeable poly (MPC-co-DMA) (PMD) membrane was placed on the other surface of the electrodes. The GOx was also immobilized using PMD solution casting onto hydrogen peroxide electrode. The calibration range for glucose solution includes the tear glucose concentration of normal subject (0.14 mmol/l). Using the same materials and procedure, this group developed soft contact lens for non-invasive and in situ monitoring of tear glucose [79]. The contact lens biosensor showed a good relationship between the output current and glucose concentration in a range of 0.03–5.0 mM, with a correlation coefficient of 0.999. The biosensor was applied to a rabbit for tear glucose monitoring. The results of tear glucose monitoring showed that tear glucose level increased with a delay of 10 min from blood sugar level.

In a recent study, a breathable flexible glucose biosensor with excellent flexibility and moisture/air permeability was developed [80]. The biosensor's electrodes were fabricated by inkjet printing method onto a flexible porous nanofiber polyimide substrate obtained through electrospinning (Fig. 5a). Graphene and platinum nanoparticles (PtNPs) were used to build three-dimensional nanostructures on the surface of the working electrode to increase specific surface area and enhance the sensing performance. Prussian blue was used to reduce the working potential, shielding the effect of interferents. The porous structure of the nanofiber substrate made the biosensor breathable, usefully inhibiting the body-fluid accumulation that could remarkably affect measurement accuracy in long-term wearable glucose monitoring. Moreover, the porous structure allowed the electrodes to be embedded within it. The array substrate was attached to a volunteer's leg skin for 12 h and no sweat accumulation was observed.

Using one-step laser-scribed PtNPs nanostructured 3D porous laser-scribed graphene (LSG), a flexible electrochemical sensing platform was developed for glucose and pH detection [81]. The prepared nanocomposites simultaneously had a hierarchical porous graphene architecture, while PtNPs significantly increased their sensitivity and electrocatalytic activity. For the fabrication of electrodes, Pt-hydroxyethyl cellulose (HEC) hydrogel was prepared and coated on the polyimide (PI) film. Laser scribing was used to fabricate super hydrophilic and co-doped LSG PtNPs. The Pt-HEC/LSG electrode was immersed in ultrapure water to remove the unetched hydrogel. The PtNP-LSG electrode was patterned by a $CO_2$ direct scribing laser machine. Finally, GOx was immobilized on the Pt-HEC/LSG working electrode and biosensor was used for glucose monitoring in sweat.


(a)
(b)
(c)
Sweat
ISF
Dual Iontophoresis
Sweat Alcohol
ISF Glucose
Screen printed
tattoo electrode
Wireless flexible electronics
Sweat
Interstitial fluid
Iontophoretic
delivery
Iontophoretic
extraction
P+Pilocarpine
Glucose
IP : Iontophoresis
Anions
Cations
(d)
counter electrode
Reference electrode
working electrode
Iontophoresis
electrode
CA/β-CD NFs
Coated GOx
Prussian Blue
Anode
Cathode
sweet glucose
skin
Current
~2mA

◀**Fig. 5** **a** A schematic representation of different steps of fabricating flexible glucose biosensor using porous nanofiber polyimide substrate, (1) the glucose biosensor, (2) substrate development, (3) images of the substrate (I) before and (II) after thermal imidization, (4) the structure of (I) three-electrode and (II) working electrode, (5) the electrode construction steps, (6) physical images that exhibit the (I) glucose biosensor and (II) flexibility of the biosensor. Reprinted from Ref. [80] with permission; **b** A schematic representation of the fabrication of PEDOT:PSS/DF/PB/GOx biosensor for the glucose monitoring in serum and the non-invasive glucose determination in ISF on human skin relying on the reverse iontophoresis, and a comparison with the glucose assay by a commercial glucometer. Reprinted from Ref. [83] with permission; **c** Simultaneous non-invasive sampling and monitoring of ISF and sweat using a wearable iontophoretic biosensor on a printed tattoo platform for glucose and alcohol measurement. Reprinted from Ref. [88] with permission; **d** A schematic illustration of iontophoresis printable electrodes and iontophoresis mechanism on the epidermal cellulose/ β-cyclodextrin /GOx nanofibers (NFs) glucose biosensor. Reprinted from Ref. [91] with permission

Conducting polymers with high flexibility and stretchability close to those of traditional plastics, and also high speed of electron transfer are interesting substrate [82]. Poly (3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) is one of the most widely studied conducting polymer for flexible and wearable glucose sensor [83, 84]. PEDOT partially aggregates and forms a “hard” conductive network in the soft PSS matrix due to the weak electrostatic interaction between PSS and PEDOT [71]. An electrochemical biosensor based on PEDOT:PSS conductive hydrogel incorporated with Prussian blue nanoparticles (PBNPs) was developed for the non-invasive and continuous monitoring of ISF glucose on human skin based on the reverse iontophoresis (RI) extraction [83]. The PEDOT:PSS hydrogel was used as a skin patch for the improvement of contact between the sensor and the skin, while its high conductivity resulted in the achievement of high sensitivity. The PBNPs and GOx were embedded into the hydrogel solution followed by the drop-coating on the working electrode and RI electrode of the screen-printed carbon electrodes (SCPE), which resulted in the formation of glucose sensing films (Fig. 5b). The SPCE was fabricated on the PET substrate. In addition to working electrode, counter electrode, and the Ag/AgCl reference electrode, the SCPE included a RI electrode with a diameter of 1 cm.

In another attempt for developing flexible electrodes, a nanocomposite film based on polyaniline (PANI) and nitrogen-doped graphene quantum dots (N-GQDs) was prepared and deposited on the SPCE fabricated on PET [85]. PANI was chosen as the matrix for GOx due to its flexibility and excellent binding for GOx, where N-GQDs supplied N-rich functional groups that act as electron transfer agents. This overcomes the electrical conductivity issues in neutral electrolytes and increases the electrical activity towards glucose detection. After the GOx immobilization, GOx/N-GQDs/PANI-based biosensor exhibited excellent performance and enhanced sensitivity for glucose detection in artificial sweat.

Wearable electrochemical biosensors have also been integrated with low cost paper-based materials and directly applied on human skin for non-invasive analyzes [86]. The use of a flexible and hydrophilic cellulose paper substrate has a significant

effect on the absorption and dispersion of active substances and increases the permeation of sweat as well as its diffusion from the human-device interface [87]. In the case of paper, tattoo-based paper sensors show high flexibility, printability, stability, and adhesion ability to human skin. They can be employed as wearable epidermal sensing devices. Kim et al. (2018) developed a flexible tattoo paper dual-electrode wearable biosensor for simultaneous and independent sampling and analysis of two epidermal biofluids (ISF and sweat) for the monitoring of glucose and alcohol [88]. The dual sampling and analysis were performed through the parallel operation of reverse iontophoretic ISF extraction across the skin and iontophoretic delivery of a sweat-inducing drug (pilocarpine) into the skin at separate positions (Fig. 5c). The wearable system was fabricated on epidermal temporary tattoo platform through screen-printing technique for disposable single use. This tattoo paper biosensor was able to measure ISF glucose at the cathode side using a glucose GOx and sweat alcohol at the anode side using an alcohol oxidase (AOx). In addition to the previously mentioned advantages of paper substrate, other advantages include the self-absorption of sweat through the created microfluidic channels in paper-based devices using the hydrophilic and hydrophobic material modification, wax printing, inkjet printing, and photolithography. Moreover, the softness and folding ability of papers are also suitable for reducing the size of the device and making devices with multiple functions [87]. In this context, a highly integrated sensing paper (HIS paper) was developed for fast sweat collection and glucose determination [87]. The HIS paper was assembled from a combination of hydrophobic protective wax, conductive electrodes, and MXene/methylene blue ($Ti_3C_2T_x$/MB) hybrid active materials by using a simple printing process. Carbon paste and silver paste were employed as counter electrode and reference electrode, respectively. Carbon paste was used to construct screen-printing carbon working electrode (SPCE). The printed paper was folded into a multi-layered structure, where a sensible three-dimensional perspiration diffusion pathway was created by connecting the hydrophilic zones of each layer, providing efficient paths for perspiration collection and diffusion of sweat along the vertical direction of the folded HIS paper. Moreover, the independent three-dimensional positioning of the three electrodes facilitated the decoration and immobilization of enzymes (GOx and lactate oxidase) as well as the accessibility of electrolytes. The unique design of the three-dimensional structure enhanced the absorption of sweat from the surface of the skin, and prevented the accumulation of liquid, thereby reducing the discomfort caused by sweat in the human–machine interface.

Hydrogels can have a homologous contact with the human body because their mechanical features are similar to the interfaces between human skin and underlying tissue [89]. Hydrogel-fibrous materials with high surface-to-volume ratio, flexibility, and high-water absorption properties are good candidates in glucose sensing wearable devices. They can be fabricated by electrospinning technique with a variety of porosity and diameters [4]. In this regard, Kim et al. (2019) developed poly(vinyl alcohol)/β-cyclodextrin hydrogels cross-linked by citric acid for glucose measurement. The GOx was physically entrapped within the β-cyclodextrin cavity for accurate detection of ISF glucose levels. The developed hydrogel system showed great potential as a patch sensor for non-invasive glucose monitoring [90].

Another advantage of hydrogels is that electrodes could be easily printed on the surface of fibrous hydrogels for wearable electrochemical devices. Kim et al. (2019) developed a cellulose/β-cyclodextrin electrospun immobilized GOx patch with reverse iontophoresis for non-invasive monitoring of ISF glucose levels. Carbon-Ag/AgCl-carbon: working-reference-counter electrode coated Prussian Blue were screen-printed on the surface of the fabricated path (Fig. 5d). The nanoporous structure of the patch was able to keep the extracted solution on the body [91]. In an interesting study with a combination of hydrogel and paper, a hydrogel paper patch (HPP) with highly porous conductive PEDOT:PSS hydrogel self-assembled on paper fiber was developed [92]. To fabricate electrode, HPP with microfluidic channels was prepared on a filter paper using a wax printer. Carbon paste and Ag/AgCl paste were printed individually on the specific areas of filter paper using screen-printing method to fabricate the counter and reference electrodes respectively. To prepare the working electrode of the glucose sensor, PEDOT:PSS solution was casted on a rectangular area. After the filter paper was completely filled with the PEDOT:PSS solution, the filter paper was soaked in dodecylbenzene sulfonic acid (DBSA) to form the PEDOT:PSS conductive hydrogel. Then, PtNPs were electrodeposited onto paper-based hydrogel. Finally, GOx was dropped on the working electrode and cross-linked with glutaraldehyde. Due to the easy processability of paper and the conductivity of PEDOT:PSS hydrogels, the proposed HPP conductivity sensing system is promising as a disposable and low cost sensor kit for health care and glucose monitoring.

Several other examples of flexible electrodes employed in wearable CGM devices are listed in Table 1.

Besides selecting the flexible substrate, electrode fabrication technique is of great importance. The electrically conductive or non-conductive substrates can be modified with different methods to create sensor electrodes. Electrodes including sensing (working), counter and reference electrodes are designed and fabricated on a flexible substrate. The materials chosen to make the electrode should have good adhesion to the substrate to create a flexible sensor. Furthermore, different kinds of nanomaterials can be used in the sensing zone of sensor to increase sensitivity and performance. Various nano/microfabrication techniques including printing (e.g., screen-printing, inkjet printing and 3D printing), laser induction, photolithography, electrodeposition, seed mediated and dealloying methods have been studied and used for the fabrication of wearable devices [4]. Among these methods, screen-printing techniques are the most common methods in the fabrication of wearable electrochemical glucose biosensors [93]. This method is extensively applied for printing conductive or non-conductive inks on flexible substrates.

## 3 Wearable Self-powered Electrochemical CGM Systems

Although conventional electrochemical batteries are the important source of the electricity required for wearable devices, they suffer from several limitations such as large size, discomfortability to wear the sensor, need to recharge and regular

**Table 1** Several examples of flexible electrodes employed in wearable CGM devices

| Flexible substrate | Working electrode | Fabrication method | Biofluid | Sensitivity | Linear range | Refs. |
|---|---|---|---|---|---|---|
| Polyethylene terephthalate (PET) | GOx-Chitosan/ CNTs-PB-Gold | UV mediated chemical plating | Sweat | 22.05 $\mu A\ mM^{-1}\ cm^{-2}$ | 0.02– 1.11 mM | [104] |
| Paper and PET | GOx-Chitosan-Nafion-PB/ Graphite ink- Ag/AgCl ink | Screen-printing | Sweat | 35.7 $\mu A\ mM^{-1}\ cm^{-2}$ | 0–1.9 mM | [105] |
| Polyimide | Nafion-GOx/ Chitosan-AuPtNPs-rGO | Photolithography and wet etching | Sweat | 45 $\mu A\ mM^{-1}\ cm^{-2}$ | 0–2.4 mM | [106] |
| Polyimide | GOx-PB-Au NPs-Gold | Electrodeposition and photolithography | Sweat | 26.31 $\mu A\ mM^{-1}\ cm^{-2}$ | 1–600 $\mu M$ | [107] |
| EcoFlex elastomer | Chitosan-GOx/ CNTs-PB-AuNWs | Seed mediated method | Sweat | 23.72 $\mu A\ mM^{-1}\ cm^{-2}$ | 0–800 $\mu M$ | [108] |
| Polyurethane modified by poly(ethylene glycol) | GOx/Chitosan- PtNPs-Gold | Photolithography and magnetron sputtering | Serum | 3.418 $\mu A\ mM^{-1}$ | 0.5–2.5 mM | [109] |
| PDMS | GOx/Chitosan/PB-Ni–Co MOF nanosheets-Gold | Chemical deposition | Sweat | 205.1 $\mu A\ mM^{-1}\ cm^{-2}$ | 0.02–0.79 mM | [110] |
| Agarose hydrogel | Nafion- GOx/Chitosan-PB-PEDOT NC-SPCE | Electrochemical deposition | Sweat | 0.2 mA | 6.25 $\mu M$–0.8 mM | [111] |
| AuNWs/SEBS fiber | GOx/Chitosan/PB | Dry spinning and electroless plating | Sweat | 11.7 $\mu A\ mM^{-1}\ cm^{-2}$ | 0–500 $\mu M$ | [112] |
| Parylene | Gox-AgNWs-Graphene | Photolithography | Tear | – | 1 $\mu M$–10 mM | [113] |

CNTs: carbon nanotubes; PB: Prussian blue; rGO: reduced graphene oxide; AuNWs: gold nanowires; MOF: Metal–organic framework; PB-PEDOT NC: Prussian blue-doped poly(3,4-ethylenedioxythiophene nanocomposite; SPCE: Screen-printed carbon electrode; SEBS: Styrene-ethylene/butylene-styrene

replacement. Therefore, multiple wearable energy harvesters including electrostatic, thermoelectric, electromagnetic, piezoelectric and triboelectric power have been developed. Self-powered energy harvesters may convert numerous forms of environmental energy into electrical energy and can partially replace batteries. Compared to the conventional batteries, self-powered energy harvesters are inexpensive, compact, lightweight and environmentally friendly. The energy that is harvested can come from body movements, body temperature, human physiological processes, surrounding environment, solar energy and artificial light [94, 95]. In addition to mechanical energy, in self-powered wearable biosensors, chemical energy from the components secreted from body fluids such as glucose or lactate can be used as energy source and converted to electrical energy. Since fiber-based textiles are the most popular material for human clothing, they can be used as interesting materials for wearable biosensors. Micro-cable structured textiles with light weight and high flexibility have been used to harvest energy from mechanical excitation, wind blowing and chemical energy (from body secreted materials). Textile- and paper-based chemical energy converters are also known as biofuel cells. A wearable and flexible textile-based glucose biofuel cell by polyester-based employing moisture management fabric (MMF), which is extensively used in sportswear, was proposed by Wang et al. (2020). In this system, MMF as electrolyte and biofuel transport media were located between two carbon-based components that served as cathode and anode. PB and GOx were immobilized onto cathode and anode, respectively (Fig. 6a). The reduction of PB-modified cathode was driven by the oxidation of glucose catalyzed by GOx-modified anode, and this enables a single-compartment structure where MMF acts as biofuel transport media. Because MMF was made of polyester, it naturally induced a continuous and high speed flow which facilitated molecule transport for efficient chemical reactions without an additional pump. With this system, glucose was detected in the range of 0.1–1 mM [96]. In another study, a self-powered glucose biosensor was developed by embedding self-powered bioelectronics on a mask that measured the biological glucose signal with continuous energy (Fig. 6b) [97]. The fabrication of mask-based printed electrodes was based on screen-printing technique. The bioanode and cathode of the printed electrode on the medical mask were modified with highly capacitive materials including conducting polymers of PEDOT and PANI and nanomaterials of carbon nanotubes (CNTs). The electrode modification significantly increased capacitive properties on the electrode surfaces to store charges. The PANI-modified bioanode was functionalized with GOx and tetrathiafulvalene. When glucose in sweat came into contact with GOx on the surface of the flexible mask-based bioanode, the bioanode generated electrons. These electrons produced by glucose oxidation on the bioanode then drove the self-sustainable energy system. Finally, the electrons flowed to the cathode modified with PEDOT/CNTs and completed the circuit. This mask-based flexible device could hold potential for the next generation of smart textiles and wearable devices.

Smartwatches are interesting devices for integrating with glucose biosensors. In this regard, a fully integrated and self-powered smartwatch was developed for continuous monitoring of glucose in sweat [98]. The smartwatch included flexible silicon-based photovoltaic cells for energy harvesting and conversion, flexible Zn-$MnO_2$

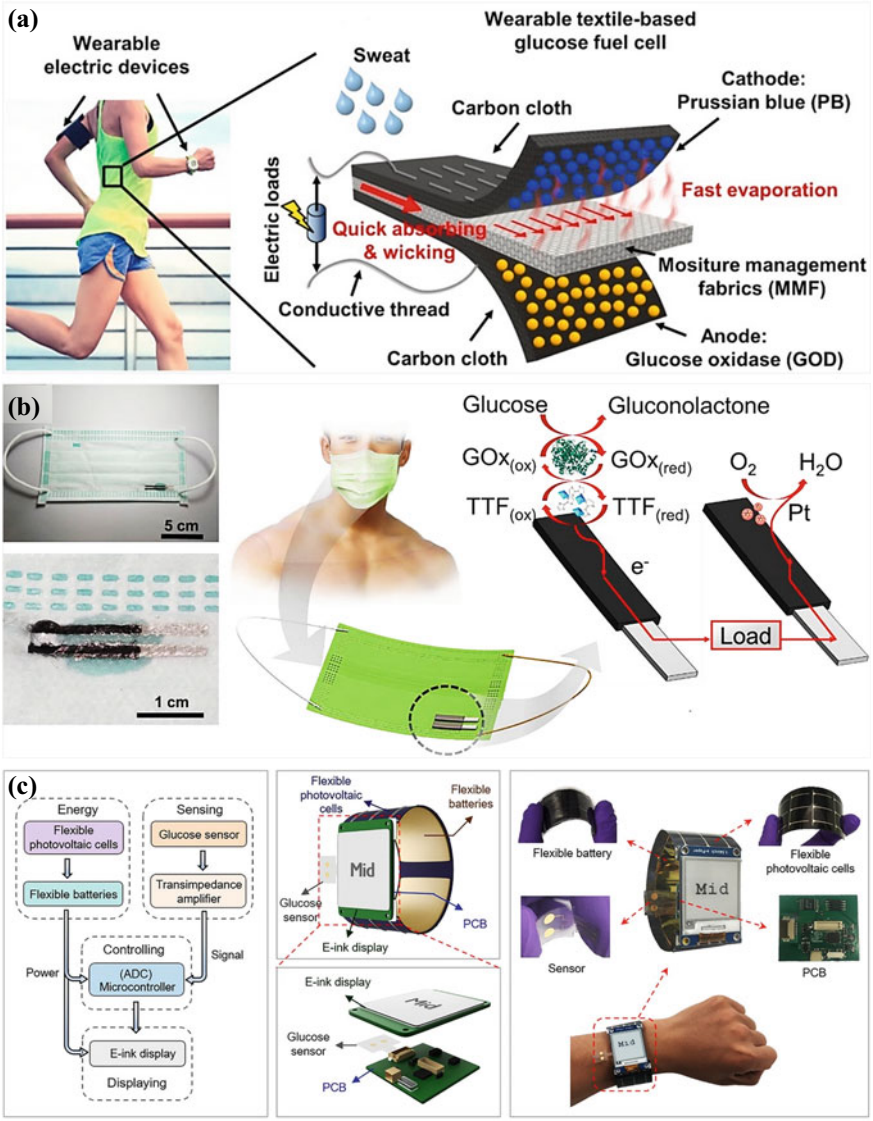



**Fig. 6** **a** A wearable textile-based glucose biofuel cell employed moisture control fabrics used in sportswear. Reprinted from Ref. [96] with permission; **b** A schematic representation of a mask-based bioelectronic system for energy capturing from glucose and self-powered measurement of glucose. Reprinted from Ref. [97] with permission; **c** A schematic illustration of the totally combined self-powered smartwatch for continuous determination of glucose; from left to right respectively: System-level block layout of the self-powered smartwatch; schematic representation of the self-powered smartwatch; and pictures of the smartwatch on an individual's wrist and separate parts. Reprinted from Ref. [98] with permission

rechargeable batteries as intermediate energy storage devices, an electrochemical glucose sensor, a printed circuit board (PCB) as a controlling module, and electronic ink (E-ink) display to facilitate direct and real-time monitoring in the form of a "watch strap". In the sensing part, two electrodes including working and reference/counter electrodes were fabricated on flexible PET polymer using photolithography and thermally evaporated nano-layers of Cr/Au. The electrolyte made of polyvinyl alcohol (PVA) was located between $MnO_2$@ nitrogen-doped carbon foams (N-CF) cathode and Zn@N-CF anode (Fig. 6c). In this system, the sweat extraction was based on the iontophoresis method. This smartwatch showed a good performance in glucose detection.

## 4 Comparison of Glucose Detection in Sweat and ISF

Recent efforts have focused on epidermal biomonitoring devices of two easily accessible biofluids including ISF and sweat. Reliable and convenient non-invasive monitoring of desired biomarkers in these biofluids could potentially have a major influence on a wide range of health and wellness applications. Sweat contains several biomarkers that reflect the physiological state of the blood, as they are released from the bloodstream through sweat [88]. The presence of blood-related biomarkers in sweat, non-invasiveness, continuous monitoring, easy collection and its easier accessibility than ISF makes it an ideal medium for non-invasive biomarker monitoring. However, one of the limitations of sweat is that it can only be evaluated once it is excreted to the outer surface of the skin and several available methods for sweat generation (e.g. thermal heating, prolonged exercise, stress, and iontophoretic stimulation) can be both time-consuming, and cumbersome and discomfort when dealing with diabetic patients, and ultimately cause the loss of the benefits of using sweat as a matrix biomarker detection. Moreover, skin surface glucose can confound these measurements. On the other hand, despite some reports on the correlation between sweat and blood glucose [99], it's not specified yet whether sweat glucose concentration reflects the metabolic status of the users. In addition to the lack of a good correlation between sweat and blood glucose levels, as well as the difficulty of sweat collection, other limitations of sweat include variation in GOx activity due to lactic acid secretion and environmental temperature changes and enzyme delamination when exposed to mechanical friction and skin deformation. Relatively low sensitivity due to lower glucose concentration in sweat and distinct hysteresis compared to blood glucose level are also the main aspects limiting its use [77]. ISF is of particular importance because of high glucose content in ISF (the glucose concentration in blood ranges from 2 ~ 40 mmol/L, in ISF is 1.99 ~ 22.2 mmol/L, in sweat is 0.01 ~ 1.11 mmol/L) [100], good stability (compared to the discontinuous and unstable secretion of sweat), good linear range, high sensitivity, and high correlation coefficient with blood glucose levels due to its proximity to blood capillaries, which allows for rapid diffusion from the blood into the ISF. Moreover, the detection of glucose levels in ISF possesses mature technologies since several commercial devices have

been developed [101–103]. Thus, accuracy of ISF analysis in much better than other biofluids (i.e. tear, saliva and sweat). However, a suitable element to pierce the stratum corneum and reach the epidermis and dermis is required for accurate ISF measurement [66]. In this regard, MNs can be used for both ISF extraction and ISF analysis. A less invasive or even non-invasive alternative approach to avoid piercing the skin is the employing reverse iontophoresis method to extract ISF. However, the latter method may cause skin irritation [66]. The other challenge with ISF application is that since the material exchange between blood and ISF exists for a certain period of time, the measured results often lag behind, and may not reflect the real-time value of blood glucose [77]. Regarding the comparison of the sensitivity of wearable sensors based on sweat or interstitial fluid, it should be mentioned that it is not possible to say with certainty which one is more sensitive, since the sensitivity depends on various factors, including the elements used in the sensor's construction. However, we have to notice to the presence of quite low levels of sweat glucose and, thus, the need to develop devices with higher sensitivity. In this context, a combination of some specific materials has shown that the increased surface area and porosity provided, for example, by nanofibers or nanoparticle-modified electrodes, can improve sensor performance with high sensitivity, low LOD, and wide linear range. For commercial development of sweat-based sensors, in vivo validation tests are still required for meaningful medical applications to investigate the correlation of sweat with blood readings.

## 5 Conclusions

Continuous monitoring of glucose using wearable devices is considered as an ideal approach to control glucose levels in diabetic individuals. Most commercially available CGM devices that have received FDA approval are based on the principle of electrochemical glucose sensing due to high accuracy and sensitivity. Two groups of wearable devices including minimally invasive and non-invasive sensors based on glucose in tears, sweat, saliva and urine have become of great interest to researchers. In this regard, the possibility of using different biofluids as detection samples and also innovative monitoring devices including microneedle arrays, flexible electrode-based sensors and data transmission systems including wireless and self-powered have been studied in recent years. However, despite recent advances in wearable biosensors, commercialized wearable devices still face considerable challenges. Several limitations such as high production costs and inflexible and uncomfortable tools with the human body have prevented the widespread use of these health care monitoring devices in the daily life of diabetic people. Development of flexible materials with high surface area, special mechanical characteristics, and adaptability to the human body has opened new avenues in innovative glucose monitoring devices. Therefore, it is still necessary to understand as much as possible the characteristics of these materials in order to use them properly and use appropriate technology to fabricate wearable glucose monitoring devices. In addition, considerable attention is being paid

to microfluidic and self-powered/sustainable devices based on flexible materials to reduce manufacturing costs and increase device compatibility, stability, and applicability. Another interesting topic regarding wearable glucose monitoring devices is the development of multiplexed monitoring systems that are able to measure other diabetes-related biomarkers to provide a better assessment of diabetes treatment and improve the life quality of diabetic patients. It is also necessary to mention that not only CGM devices can be used for monitoring purposes but also they have the potential for therapeutic applications with a combination of closed-loop systems for insulin infusion in individuals with type I diabetes, i.e., an artificial pancreas. The next generation of wearable CGM devices can certainly provide more accurate and unique glucose monitoring capabilities for diabetic patients.

## References

1. Wang, J.: Electrochemical glucose biosensors. Chem. Rev. **108**(2), 814–825 (2008). https://doi.org/10.1021/cr068123a
2. Yoo, E.-H., Lee, S.-Y.: Glucose biosensors: an overview of use in clinical practice. Sensors **10**(5), 4558–4576 (2010). https://doi.org/10.3390/s100504558
3. Sehit, E., Altintas, Z.: Biosensors for glucose detection. In: Advanced Sensor Technology, pp. 235–259. Elsevier (2023)
4. Sanati, A., Esmaeili, Y., Bidram, E., Shariati, L., Rafienia, M., Mahshid, S., Parlak, O.: Recent advancement in electrode materials and fabrication, microfluidic designs, and self-powered systems for wearable non-invasive electrochemical glucose monitoring. Appl. Mater. Today **26**, 101350 (2022). https://doi.org/10.1016/j.apmt.2021.101350
5. Teymourian, H., Parrilla, M., Sempionatto, J.R., Montiel, N.F., Barfidokht, A., Van Echelpoel, R., De Wael, K., Wang, J.: Wearable electrochemical sensors for the monitoring and screening of drugs. ACS Sens. **5**(9), 2679–2700 (2020). https://doi.org/10.1021/acssensors.0c01318
6. Zhang, S., Zhao, W., Zeng, J., He, Z., Wang, X., Zhu, Z., Hu, R., Liu, C., Wang, Q.: Wearable non-invasive glucose sensors based on metallic nanomaterials. Mater. Today Bio. 100638 (2023). https://doi.org/10.1016/j.mtbio.2023.100638
7. Zafar, H., Channa, A., Jeoti, V., Stojanović, G.M.: Comprehensive review on wearable sweat-glucose sensors for continuous glucose monitoring. Sensors **22**(2), 638 (2022). https://doi.org/10.3390/s22020638
8. Heifler, O., Borberg, E., Harpak, N., Zverzhinetsky, M., Krivitsky, V., Gabriel, I., Fourman, V., Sherman, D., Patolsky, F.: Clinic-on-a-needle array toward future minimally invasive wearable artificial pancreas applications. ACS Nano **15**(7), 12019–12033 (2021). https://doi.org/10.1021/acsnano.1c03310
9. Mohammadpour-Haratbar, A., Mohammadpour-Haratbar, S., Zare, Y., Rhee, K.Y., Park, S.-J.: A review on non-enzymatic electrochemical biosensors of glucose using carbon nanofiber nanocomposites. Biosensors **12**(11), 1004 (2022). https://doi.org/10.3390/bios12111004
10. Naikoo, G.A., Salim, H., Hassan, I.U., Awan, T., Arshad, F., Pedram, M.Z., Ahmed, W., Qurashi, A.: Recent advances in non-enzymatic glucose sensors based on metal and metal oxide nanostructures for diabetes management-a review. Front. Chem. **9**, 748957 (2021). https://doi.org/10.3389/fchem.2021.748957
11. Price, C.P.: Point-of-care testing in diabetes mellitus. Clin. Chem. Lab. Med. **41**, 1213–1219 (2003). https://doi.org/10.1515/CCLM.2003.185
12. Heller, A., Feldman, B.: Electrochemical glucose sensors and their applications in diabetes management. Chem. Rev. **108**(7), 2482–2505 (2008). https://doi.org/10.1021/cr068069y

13. Bankar, S.B., Bule, M.V., Singhal, R.S., Ananthanarayan, L.: Glucose oxidase—an overview. Biotechnol. Adv. **27**(4), 489–501 (2009). https://doi.org/10.1016/j.biotechadv.2009.04.003
14. Jeon, W.-Y., Kim, H.-H., Choi, Y.-B.: Development of a glucose sensor based on glucose dehydrogenase using polydopamine-functionalized nanotubes. Membranes **11**(6), 384 (2021). https://doi.org/10.3390/membranes11060384
15. Ferri, S., Kojima, K., Sode, K.: Review of glucose oxidases and glucose dehydrogenases: a bird's eye view of glucose sensing enzymes. J. Diabetes Sci. Technol. **5**(5), 1068–1076 (2011). https://doi.org/10.1177/193229681100500507
16. Jeon, W.-Y., Hyug-Han Kim, C.-J., Choi, Y.-B., Lee, B.-H., Jo, H.-J., Jeon, S.-Y.: Glucose detection via Ru-mediated catalytic reaction of glucose dehydrogenase. Adv. Mater. Lett. **9**(3), 220–224 (2018). https://doi.org/10.5185/amlett.2018.1947
17. Lee, I., Probst, D., Klonoff, D., Sode, K.: Continuous glucose monitoring systems-current status and future perspectives of the flagship technologies in biosensor research. Biosens. Bioelectron. **181**, 113054 (2021). https://doi.org/10.1016/j.bios.2021.113054
18. Karyakin, A.A., Gitelmacher, O.V., Karyakina, E.E.: Prussian blue-based first-generation biosensor. A sensitive amperometric electrode for glucose. Anal. Chem. **67**(14), 2419–2423 (1995). https://doi.org/10.1021/ac00110a016
19. Wang, J.: Glucose biosensors: 40 years of advances and challenges. Electroynalysis (N.Y.N.Y.) **13**(12), 983–988 (2001). https://doi.org/10.1002/1521-4109(200108)13:12<983::AID-ELAN983>3.0.CO;2-%23
20. Hassan, M.H., Vyas, C., Grieve, B., Bartolo, P.: Recent advances in enzymatic and non-enzymatic electrochemical glucose sensing. Sensors **21**(14), 4672 (2021). https://doi.org/10.3390/s21144672
21. Teymourian, H., Moonla, C., Tehrani, F., Vargas, E., Aghavali, R., Barfidokht, A., Tangkuaram, T., Mercier, P.P., Dassau, E., Wang, J.: Microneedle-based detection of ketone bodies along with glucose and lactate: toward real-time continuous interstitial fluid monitoring of diabetic ketosis and ketoacidosis. Anal. Chem. **92**(2), 2291–2300 (2019). https://doi.org/10.1021/acs.analchem.9b05109
22. Ahmed, M.U., Hossain, M.M., Tamiya, E.: Electrochemical biosensors for medical and food applications. Electroynalysis (N.Y.N.Y.) **20**(6), 616–626 (2008). https://doi.org/10.1002/elan.200704121
23. Teymourian, H., Barfidokht, A., Wang, J.: Electrochemical glucose sensors in diabetes management: an updated review (2010–2020). Chem. Soc. Rev. **49**(21), 7671–7709 (2020). https://doi.org/10.1039/D0CS00304B
24. Suzuki, N., Lee, J., Loew, N., Takahashi-Inose, Y., Okuda-Shimazaki, J., Kojima, K., Mori, K., Tsugawa, W., Sode, K.: Engineered glucose oxidase capable of quasi-direct electron transfer after a quick-and-easy modification with a mediator. Int. J. Mol. Sci. **21**(3), 1137 (2020). https://doi.org/10.3390/ijms21031137
25. Dong, S., Wang, B., Liu, B.: Amperometric glucose sensor with ferrocene as an electron transfer mediator. Biosens. Bioelectron. **7**(3), 215–222 (1992). https://doi.org/10.1016/0956-5663(92)87018-K
26. Cass, A.E., Davis, G., Francis, G.D., Hill, H.A.O., Aston, W.J., Higgins, I.J., Plotkin, E.V., Scott, L.D., Turner, A.P.: Ferrocene-mediated enzyme electrode for amperometric determination of glucose. Anal. Chem. **56**(4), 667–671 (1984). https://doi.org/10.1021/ac00268a018
27. Bruen, D., Delaney, C., Florea, L., Diamond, D.: Glucose sensing for diabetes monitoring: recent developments. Sensors **17**(8), 1866 (2017). https://doi.org/10.3390/s17081866
28. Goodnight, L., Butler, D., Xia, T., Ebrahimi, A.: Non-enzymatic detection of glucose in neutral solution using PBS-treated electrodeposited copper-nickel electrodes. Biosensors **11**(11), 409 (2021). https://doi.org/10.3390/bios11110409
29. Niu, X., Shi, L., Zhao, H., Lan, M.: Advanced strategies for improving the analytical performance of Pt-based nonenzymatic electrochemical glucose sensors: a minireview. Anal. Methods **8**(8), 1755–1764 (2016). https://doi.org/10.1039/C5AY03181H

30. Shim, K., Lee, W.-C., Park, M.-S., Shahabuddin, M., Yamauchi, Y., Hossain, M.S.A., Shim, Y.-B., Kim, J.H.: Au decorated core-shell structured Au@ Pt for the glucose oxidation reaction. Sens. Actuators B: Chem. **278**, 88–96 (2019). https://doi.org/10.1016/j.snb.2018.09.048
31. Abunahla, H., Mohammad, B., Alazzam, A., Jaoude, M.A., Al-Qutayri, M., Abdul Hadi, S., Al-Sarawi, S.F.: MOMSense: metal-oxide-metal elementary glucose sensor. Sci. Rep. **9**(1), 5524 (2019). https://doi.org/10.1038/s41598-019-41892-w
32. Zhu, H., Li, L., Zhou, W., Shao, Z., Chen, X.: Advances in non-enzymatic glucose sensors based on metal oxides. J. Mater. Chem. B **4**(46), 7333–7349 (2016). https://doi.org/10.1039/C6TB02037B
33. Rahman, M.M., Saleh Ahammad, A., Jin, J.-H., Ahn, S.J., Lee, J.-J.: A comprehensive review of glucose biosensors based on nanostructured metal-oxides. Sensors **10**(5), 4855–4886 (2010). https://doi.org/10.3390/s100504855
34. Zhang, Y., Su, L., Manuzzi, D., de los Monteros, H.V.E., Jia, W., Huo, D., Hou, C., Lei, Y.: Ultrasensitive and selective non-enzymatic glucose detection using copper nanowires. Biosens. Bioelectron. **31**(1), 426–432 (2012). https://doi.org/10.1016/j.bios.2011.11.006
35. Yi, W., Liu, J., Chen, H., Gao, Y., Li, H.: Copper/nickel nanoparticle decorated carbon nanotubes for nonenzymatic glucose biosensor. J. Solid State Electrochem. **19**, 1511–1521 (2015). https://doi.org/10.1007/s10008-015-2766-2
36. Phetsang, S., Kidkhunthod, P., Chanlek, N., Jakmunee, J., Mungkornasawakul, P., Ounnunkad, K.: Copper/reduced graphene oxide film modified electrode for non-enzymatic glucose sensing application. Sci. Rep. **11**(1), 9302 (2021). https://doi.org/10.1038/s41598-021-88747-x
37. Fall, B., Sall, D.D., Hémadi, M., Diaw, A.K.D., Fall, M., Randriamahazaka, H., Thomas, S.: Highly efficient non-enzymatic electrochemical glucose sensor based on carbon nanotubes functionalized by molybdenum disulfide and decorated with nickel nanoparticles (GCE/CNT/MoS2/NiNPs). Sens. Actuators Rep. **5**, 100136 (2023). https://doi.org/10.1016/j.snr.2022.100136
38. Fang, L., Wang, F., Chen, Z., Qiu, Y., Zhai, T., Hu, M., Zhang, C., Huang, K.: Flower-like $MoS_2$ decorated with $Cu_2O$ nanoparticles for non-enzymatic amperometric sensing of glucose. Talanta **167**, 593–599 (2017). https://doi.org/10.1016/j.talanta.2017.03.008
39. Khan, A., Khan, A.A.P., Marwani, H.M., Alotaibi, M.M., Asiri, A.M., Manikandan, A., Siengchin, S., Rangappa, S.M.: Sensitive non-enzymatic glucose electrochemical sensor based on electrochemically synthesized PANI/bimetallic oxide composite. Polymers **14**(15), 3047 (2022). https://doi.org/10.3390/polym14153047
40. Osuna, V., Vega-Rios, A., Zaragoza-Contreras, E.A., Estrada-Moreno, I.A., Dominguez, R.B.: Progress of polyaniline glucose sensors for diabetes mellitus management utilizing enzymatic and non-enzymatic detection. Biosensors **12**(3), 137 (2022). https://doi.org/10.3390/bios12030137
41. Cappon, G., Acciaroli, G., Vettoretti, M., Facchinetti, A., Sparacino, G.: Wearable continuous glucose monitoring sensors: a revolution in diabetes treatment. Electronics **6**(3), 65 (2017). https://doi.org/10.3390/electronics6030065
42. Vaddiraju, S., Burgess, D.J., Tomazos, I., Jain, F.C., Papadimitrakopoulos, F.: Technologies for continuous glucose monitoring: current problems and future promises. J. Diabetes Sci. Technol. **4**(6), 1540–1562 (2010). https://doi.org/10.1177/193229681000400632
43. Srivastava, A., Chowdhury, M.K., Sharma, S., Sharma, N.: Blood glucose monitoring using non invasive optical method: Design limitations and challenges. Int. J. Adv. Res. Electr. Electron. Instrum. Eng. **2**(1) (2013)
44. Wang, G., He, X., Wang, L., Gu, A., Huang, Y., Fang, B., Geng, B., Zhang, X.: Non-enzymatic electrochemical sensing of glucose. Microchim. Acta **180**, 161–186 (2013). https://doi.org/10.1007/s00604-012-0923-1
45. Zhao, H., Guo, X., Wang, Y., Duan, X., Qu, H., Zhang, H., Zhang, D., Pang, W.: Microchip based electrochemical-piezoelectric integrated multi-mode sensing system for continuous glucose monitoring. Sens. Actuators B: Chem. **223**, 83–88 (2016). https://doi.org/10.1016/j.snb.2015.09.022

46. Garg, S.K., Potts, R.O., Ackerman, N.R., Fermi, S.J., Tamada, J.A., Chase, H.P.: Correlation of fingerstick blood glucose measurements with GlucoWatch biographer glucose results in young subjects with type 1 diabetes. Diabetes Care **22**(10), 1708–1714 (1999). https://doi.org/10.2337/diacare.22.10.1708
47. Johnston, L., Wang, G., Hu, K., Qian, C., Liu, G.: Advances in biosensors for continuous glucose monitoring towards wearables. Front. Bioeng. Biotechnol. **9**, 733810 (2021). https://doi.org/10.3389/fbioe.2021.733810
48. Zou, Y., Chu, Z., Guo, J., Liu, S., Ma, X., Guo, J.: Minimally invasive electrochemical continuous glucose monitoring sensors: Recent progress and perspective. Biosens. Bioelectron. 115103 (2023). https://doi.org/10.1016/j.bios.2023.115103
49. Todaro, B., Begarani, F., Sartori, F., Luin, S.: Is Raman the best strategy towards the development of non-invasive continuous glucose monitoring devices for diabetes management? Front. Chem. **10**, 1139 (2022). https://doi.org/10.3389/fchem.2022.994272
50. Acciaroli, G., Vettoretti, M., Facchinetti, A., Sparacino, G.: Calibration of minimally invasive continuous glucose monitoring sensors: state-of-the-art and current perspectives. Biosensors **8**(1), 24 (2018). https://doi.org/10.3390/bios8010024
51. Liu, Y., Yu, Q., Luo, X., Yang, L., Cui, Y.: Continuous monitoring of diabetes with an integrated microneedle biosensing device through 3D printing. Microsyst. Nanoeng. **7**(1), 75 (2021). https://doi.org/10.1038/s41378-021-00302-w
52. Xie, Z., Zhang, X., Chen, G., Che, J., Zhang, D.: Wearable microneedle-integrated sensors for household health monitoring. Eng. Regen. (2022). https://doi.org/10.1016/j.engreg.2022.09.002
53. Zhang, B.L., Zhang, X.P., Chen, B.Z., Fei, W.M., Cui, Y., Guo, X.D.: Microneedle-assisted technology for minimally invasive medical sensing. Microchem. J. **162**, 105830 (2021). https://doi.org/10.1016/j.microc.2020.105830
54. García-Guzmán, J.J., Pérez-Ràfols, C., Cuartero, M., Crespo, G.A.: Microneedle based electrochemical (Bio) Sensing: Towards decentralized and continuous health status monitoring. TrAC Trends Anal. Chem. **135**, 116148 (2021). https://doi.org/10.1016/j.trac.2020.116148
55. Sharma, S., Huang, Z., Rogers, M., Boutelle, M., Cass, A.E.: Evaluation of a minimally invasive glucose biosensor for continuous tissue monitoring. Anal. Bioanal. Chem. **408**, 8427–8435 (2016). https://doi.org/10.1007/s00216-016-9961-6
56. Samavat, S., Lloyd, J., O'Dea, L., Zhang, W., Preedy, E., Luzio, S., Teng, K.S.: Uniform sensing layer of immiscible enzyme-mediator compounds developed via a spray aerosol mixing technique towards low cost minimally invasive microneedle continuous glucose monitoring devices. Biosens. Bioelectron. **118**, 224–230 (2018). https://doi.org/10.1016/j.bios.2018.07.054
57. Mishra, R.K., Mohan, A.V., Soto, F., Chrostowski, R., Wang, J.: A microneedle biosensor for minimally-invasive transdermal detection of nerve agents. Analyst **142**(6), 918–924 (2017). https://doi.org/10.1039/C6AN02625G
58. Valdés-Ramírez, G., Li, Y.-C., Kim, J., Jia, W., Bandodkar, A.J., Nuñez-Flores, R., Miller, P.R., Wu, S.-Y., Narayan, R., Windmiller, J.R.: Microneedle-based self-powered glucose sensor. Electrochem. Commun. **47**, 58-62 (2014). https://doi.org/10.1016/j.elecom.2014.07.014
59. Bollella, P., Sharma, S., Cass, A.E., Tasca, F., Antiochia, R.: Minimally invasive glucose monitoring using a highly porous gold microneedles-based biosensor: Characterization and application in artificial interstitial fluid. Catalysts **9**(7), 580 (2019). https://doi.org/10.3390/catal9070580
60. Sharma, S., Saeed, A., Johnson, C., Gadegaard, N., Cass, A.E.: Rapid, low cost prototyping of transdermal devices for personal healthcare monitoring. Sens. Bio-Sens. Res. **13**, 104–108 (2017). https://doi.org/10.1016/j.sbsr.2016.10.004
61. Invernale, M.A., Tang, B.C., York, R.L., Le, L., Hou, D.Y., Anderson, D.G.: Microneedle electrodes toward an amperometric glucose-sensing smart patch. Adv. Healthc. Mater. **3**(3), 338–342 (2014). https://doi.org/10.1002/adhm.201300142
62. Bollella, P., Sharma, S., Cass, A.E.G., Antiochia, R.: Minimally-invasive microneedle-based biosensor array for simultaneous lactate and glucose monitoring in artificial interstitial fluid. Electroanalysis **31**(2), 374–382 (2019). https://doi.org/10.1002/elan.201800630

63. Bao, L., Park, J., Bonfante, G., Kim, B.: Recent advances in porous microneedles: materials, fabrication, and transdermal applications. Drug Deliv. Transl. Res. **12**(2), 395–414 (2022). https://doi.org/10.1007/s13346-021-01045-x
64. Ju, J., Li, L., Regmi, S., Zhang, X., Tang, S.: Microneedle-based glucose sensor platform: from vitro to wearable point-of-care testing systems. Biosensors **12**(8), 606 (2022). https://doi.org/10.3390/bios12080606
65. Ribet, F., Stemme, G., Roxhed, N.: Real-time intradermal continuous glucose monitoring using a minimally invasive microneedle-based system. Biomed. Microdevices **20**, 1–10 (2018). https://doi.org/10.1007/s10544-018-0349-6
66. Parrilla, M., Detamornrat, U., Domínguez-Robles, J., Donnelly, R.F., De Wael, K.: Wearable hollow microneedle sensing patches for the transdermal electrochemical monitoring of glucose. Talanta **249**, 123695 (2022). https://doi.org/10.1016/j.talanta.2022.123695
67. Xie, L., Zeng, H., Sun, J., Qian, W.: Engineering microneedles for therapy and diagnosis: a survey. Micromachines **11**(3), 271 (2020). https://doi.org/10.3390/mi11030271
68. Zheng, M., Zhang, Y., Hu, T., Xu, C.: A skin patch integrating swellable microneedles and electrochemical test strips for glucose and alcohol measurement in skin interstitial fluid. Bioeng. Transl. Med. e10413 (2022). https://doi.org/10.1002/btm2.10413
69. Zheng, L., Zhu, D., Wang, W., Liu, J., Thng, S.T.G., Chen, P.: A silk-microneedle patch to detect glucose in the interstitial fluid of skin or plant tissue. Sens. Actuators B: Chem. **372**, 132626 (2022). https://doi.org/10.1016/j.snb.2022.132626
70. Kai, H., Kumatani, A.: A porous microneedle electrochemical glucose sensor fabricated on a scaffold of a polymer monolith. J. Phys. Energy **3**(2), 024006 (2021). https://doi.org/10.1088/2515-7655/abe4a1
71. Yun, S.M., Kim, M., Kwon, Y.W., Kim, H., Kim, M.J., Park, Y.-G., Park, J.-U.: Recent advances in wearable devices for non-invasive sensing. Appl. Sci. **11**(3), 1235 (2021). https://doi.org/10.3390/app11031235
72. Chen, X., Song, Y., Su, Z., Chen, H., Cheng, X., Zhang, J., Han, M., Zhang, H.: Flexible fiber-based hybrid nanogenerator for biomechanical energy harvesting and physiological monitoring. Nano Energy **38**, 43–50 (2017). https://doi.org/10.1016/j.nanoen.2017.05.047
73. Sun, L., Chen, S., Guo, Y., Song, J., Zhang, L., Xiao, L., Guan, Q., You, Z.: Ionogel-based, highly stretchable, transparent, durable triboelectric nanogenerators for energy harvesting and motion sensing over a wide temperature range. Nano Energy **63**, 103847 (2019). https://doi.org/10.1016/j.nanoen.2019.06.043
74. Promphet, N., Ummartyotin, S., Ngeontae, W., Puthongkham, P., Rodthongkum, N.: Non-invasive wearable chemical sensors in real-life applications. Anal. Chim. Acta **1179**, 338643 (2021). https://doi.org/10.1016/j.aca.2021.338643
75. Dervisevic, M., Alba, M., Prieto-Simon, B., Voelcker, N.H.: Skin in the diagnostics game: Wearable biosensor nano-and microsystems for medical diagnostics. Nano Today **30**, 100828 (2020). https://doi.org/10.1016/j.nantod.2019.100828
76. Bandodkar, A.J., Wang, J.: Non-invasive wearable electrochemical sensors: a review. Trends Biotechnol. **32**(7), 363–371 (2014). https://doi.org/10.1016/j.tibtech.2014.04.005
77. Tang, L., Chang, S.J., Chen, C.-J., Liu, J.-T.: Non-invasive blood glucose monitoring technology: a review. Sensors **20**(23), 6925 (2020). https://doi.org/10.3390/s20236925
78. Kudo, H., Sawada, T., Kazawa, E., Yoshida, H., Iwasaki, Y., Mitsubayashi, K.: A flexible and wearable glucose sensor based on functional polymers with soft-MEMS techniques. Biosens. Bioelectron. **22**(4), 558–562 (2006). https://doi.org/10.1016/j.bios.2006.05.006
79. Chu, M.X., Miyajima, K., Takahashi, D., Arakawa, T., Sano, K., Sawada, S.-I., Kudo, H., Iwasaki, Y., Akiyoshi, K., Mochizuki, M.: Soft contact lens biosensor for in situ monitoring of tear glucose as non-invasive blood sugar assessment. Talanta **83**(3), 960–965 (2011). https://doi.org/10.1016/j.talanta.2010.10.055
80. Zheng, H., Chen, H., Pu, Z., Li, D.: A breathable flexible glucose biosensor with embedded electrodes for long-term and accurate wearable monitoring. Microchem. J. **181**, 107707 (2022). https://doi.org/10.1016/j.microc.2022.107707

81. Wang, Y., Guo, H., Yuan, M., Yu, J., Wang, Z., Chen, X.: One-step laser synthesis platinum nanostructured 3D porous graphene: a flexible dual-functional electrochemical biosensor for glucose and pH detection in human perspiration. Talanta **257**, 124362 (2023). https://doi.org/10.1016/j.talanta.2023.124362
82. Zhang, L., Du, W., Nautiyal, A., Liu, Z., Zhang, X.: Recent progress on nanostructured conducting polymers and composites: synthesis, application and future aspects. Sci. China Mater. **61**(3), 303–352 (2018). https://doi.org/10.1007/s40843-017-9206-4
83. Xu, C., Jiang, D., Ge, Y., Huang, L., Xiao, Y., Ren, X., Liu, X., Zhang, Q., Wang, Y.: A PEDOT: PSS conductive hydrogel incorporated with Prussian blue nanoparticles for wearable and noninvasive monitoring of glucose. Chem. Eng. J. **431**, 134109 (2022). https://doi.org/10.1016/j.cej.2021.134109
84. Ajmal Mokhtar, S.M., Alvarez de Eulate, E., Sethumadhavan, V., Yamada, M., Prow, T.W., Evans, D.R.: Electrochemical stability of PEDOT for wearable on-skin application. J. Appl. Polym. Sci. **138**(44), 51314 (2021). https://doi.org/10.1002/app.51314
85. Lin, Y.-C., Rinawati, M., Chang, L.-Y., Wang, Y.-X., Wu, Y.-T., Yen, Y.-H., Chen, K.-J., Ho, K.-C., Yeh, M.-H.: A non-invasive wearable sweat biosensor with a flexible N-GQDs/PANI nanocomposite layer for glucose monitoring. Sens. Actuators B: Chem. **383**, 133617 (2023). https://doi.org/10.1016/j.snb.2023.133617
86. Deroco, P.B., Wachholz Junior, D., Kubota, L.T.: Paper-based wearable electrochemical sensors: a new generation of analytical devices. Electroanalysis **35**(1), e202200177 (2023). https://doi.org/10.1002/elan.202200177
87. Li, M., Wang, L., Liu, R., Li, J., Zhang, Q., Shi, G., Li, Y., Hou, C., Wang, H.: A highly integrated sensing paper for wearable electrochemical sweat analysis. Biosens. Bioelectron. **174**, 112828 (2021). https://doi.org/10.1016/j.bios.2020.112828
88. Kim, J., Sempionatto, J.R., Imani, S., Hartel, M.C., Barfidokht, A., Tang, G., Campbell, A.S., Mercier, P.P., Wang, J.: Simultaneous monitoring of sweat and interstitial fluid using a single wearable biosensor platform. Adv. Sci. **5**(10), 1800880 (2018). https://doi.org/10.1002/advs.201800880
89. Sun, J.-Y., Zhao, X., Illeperuma, W.R., Chaudhuri, O., Oh, K.H., Mooney, D.J., Vlassak, J.J., Suo, Z.: Highly stretchable and tough hydrogels. Nature **489**(7414), 133–136 (2012). https://doi.org/10.1038/nature11409
90. Kim, G.J., Yoon, K.J., Kim, K.O.: Glucose-responsive poly (vinyl alcohol)/β-cyclodextrin hydrogel with glucose oxidase immobilization. J. Mater. Sci. **54**(19), 12806–12817 (2019). https://doi.org/10.1007/s10853-019-03805-0
91. Kim, K.O., Kim, G.J., Kim, J.H.: A cellulose/β-cyclodextrin nanofiber patch as a wearable epidermal glucose sensor. RSC Adv. **9**(40), 22790–22794 (2019). https://doi.org/10.1039/C9RA03887F
92. Li, T., Liang, B., Ye, Z., Zhang, L., Xu, S., Tu, T., Zhang, Y., Cai, Y., Zhang, B., Fang, L.: An integrated and conductive hydrogel-paper patch for simultaneous sensing of Chemical-Electrophysiological signals. Biosens. Bioelectron. **198**, 113855 (2022). https://doi.org/10.1016/j.bios.2021.113855
93. Sanati, A., Jalali, M., Raeissi, K., Karimzadeh, F., Kharaziha, M., Mahshid, S.S., Mahshid, S.: A review on recent advancements in electrochemical biosensing using carbonaceous nanomaterials. Microchim. Acta **186**, 1–22 (2019). https://doi.org/10.1007/s00604-019-3854-2
94. Rayegani, A., Saberian, M., Delshad, Z., Liang, J., Sadiq, M., Nazar, A.M., Mohsan, S.A.H., Khan, M.A.: Recent advances in self-powered wearable sensors based on piezoelectric and triboelectric nanogenerators. Biosensors **13**(1), 37 (2022). https://doi.org/10.3390/bios13010037
95. Zeng, X., Peng, R., Fan, Z., Lin, Y.: Self-powered and wearable biosensors for healthcare. Mater. Today Energy **23**, 100900 (2022). https://doi.org/10.1016/j.mtener.2021.100900
96. Wang, C., Shim, E., Chang, H.-K., Lee, N., Kim, H.R., Park, J.: Sustainable and high-power wearable glucose biofuel cell using long-term and high-speed flow in sportswear fabrics. Biosens. Bioelectron. **169**, 112652 (2020). https://doi.org/10.1016/j.bios.2020.112652

97. Jeerapan, I., Sangsudcha, W., Phokhonwong, P.: Wearable energy devices on mask-based printed electrodes for self-powered glucose biosensors. Sens. Bio-Sens. Res. **38**, 100525 (2022). https://doi.org/10.1016/j.sbsr.2022.100525
98. Zhao, J., Lin, Y., Wu, J., Nyein, H.Y.Y., Bariya, M., Tai, L.-C., Chao, M., Ji, W., Zhang, G., Fan, Z.: A fully integrated and self-powered smartwatch for continuous sweat glucose monitoring. ACS Sens. **4**(7), 1925–1933 (2019). https://doi.org/10.1021/acssensors.9b00891
99. Moyer, J., Wilson, D., Finkelshtein, I., Wong, B., Potts, R.: Correlation between sweat glucose and blood glucose in subjects with diabetes. Diabetes Technol. Ther. **14**(5), 398–402 (2012). https://doi.org/10.1089/dia.2011.0262
100. Peng, Z., Xie, X., Tan, Q., Kang, H., Cui, J., Zhang, X., Li, W., Feng, G.: Blood glucose sensors and recent advances: a review. J. Innov. Opt. Health Sci. **15**(02), 2230003 (2022). https://doi.org/10.1142/S1793545822300038
101. Mastrototaro, J.J.: The MiniMed continuous glucose monitoring system. Diabetes Technol. Ther. **2**(1, Supplement 1), 13–18 (2000). https://doi.org/10.1089/15209150050214078
102. Roze, S., Isitt, J., Smith-Palmer, J., Javanbakht, M., Lynch, P.: Long-term cost-effectiveness of Dexcom G6 real-time continuous glucose monitoring versus self-monitoring of blood glucose in patients with type 1 diabetes in the UK. Diabetes Care **43**(10), 2411–2417 (2020). https://doi.org/10.1007/s13300-020-00959-y
103. Feldman, B., McGarraugh, G., Heller, A., Bohannon, N., Skyler, J., DeLeeuw, E., Clarke, D.: FreeStyle™: a small-volume electrochemical glucose sensor for home blood glucose testing. Diabetes Technol. Ther. **2**(2), 221–229 (2000). https://doi.org/10.1089/15209150050025177
104. Wang, Y., Wang, X., Lu, W., Yuan, Q., Zheng, Y., Yao, B.: A thin film polyethylene terephthalate (PET) electrochemical sensor for detection of glucose in sweat. Talanta **198**, 86–92 (2019). https://doi.org/10.1016/j.talanta.2019.01.104
105. Cao, Q., Liang, B., Tu, T., Wei, J., Fang, L., Ye, X.: Three-dimensional paper-based microfluidic electrochemical integrated devices (3D-PMED) for wearable electrochemical glucose detection. RSC Adv. **9**(10), 5674–5681 (2019). https://doi.org/10.1039/c8ra09157a
106. Xuan, X., Yoon, H.S., Park, J.Y.: A wearable electrochemical glucose sensor based on simple and low-cost fabrication supported micro-patterned reduced graphene oxide nanocomposite electrode on flexible substrate. Biosens. Bioelectron. **109**, 75–82 (2018). https://doi.org/10.1016/j.bios.2018.02.054
107. Yokus, M.A., Songkakul, T., Pozdin, V.A., Bozkurt, A., Daniele, M.A.: Wearable multiplexed biosensor system toward continuous monitoring of metabolites. Biosens. Bioelectron. **153**, 112038 (2020). https://doi.org/10.1016/j.bios.2020.112038
108. Zhai, Q., Gong, S., Wang, Y., Lyu, Q., Liu, Y., Ling, Y., Wang, J., Simon, G.P., Cheng, W.: Enokitake mushroom-like standing gold nanowires toward wearable noninvasive bimodal glucose and strain sensing. ACS Appl. Mater. Interfaces **11**(10), 9724–9729 (2019). https://doi.org/10.1021/acsami.8b19383
109. Feng, R., Chu, Y., Wang, X., Wu, Q., Tang, F.: A long-term stable and flexible glucose sensor coated with poly (ethylene glycol)-modified polyurethane. J. Electroanal. Chem. **895**, 115518 (2021). https://doi.org/10.1016/j.jelechem.2021.115518
110. Shu, Y., Shang, Z., Su, T., Zhang, S., Lu, Q., Xu, Q., Hu, X.: A highly flexible Ni–Co MOF nanosheet coated Au/PDMS film based wearable electrochemical sensor for continuous human sweat glucose monitoring. Analyst **147**(7), 1440–1448 (2022). https://doi.org/10.1039/D1AN02214H
111. Lin, P.-H., Sheu, S.-C., Chen, C.-W., Huang, S.-C., Li, B.-R.: Wearable hydrogel patch with noninvasive, electrochemical glucose sensor for natural sweat detection. Talanta **241**, 123187 (2022). https://doi.org/10.1016/j.talanta.2021.123187
112. Zhao, Y., Zhai, Q., Dong, D., An, T., Gong, S., Shi, Q., Cheng, W.: Highly stretchable and strain-insensitive fiber-based wearable electrochemical biosensor to monitor glucose in the sweat. Anal. Chem. **91**(10), 6569–6576 (2019). https://doi.org/10.1021/acs.analchem.9b00152
113. Kim, J., Kim, M., Lee, M.-S., Kim, K., Ji, S., Kim, Y.-T., Park, J., Na, K., Bae, K.-H., Kyun Kim, H.: Wearable smart sensor systems integrated on soft contact lenses for wireless ocular diagnostics. Nat. Commun. **8**(1), 14997 (2017). https://doi.org/10.1038/ncomms14997