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Wearable non-invasive epidermal glucose sensors: A review☆

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ABSTRACT

The growing recent interest in wearable and mobile technologies has led to increased research efforts toward development of non-invasive glucose monitoring platforms. Continuous glucose monitoring addresses the limitations of finger-stick blood testing and provides the opportunity for optimal therapeutic interventions. This article reviews recent advances and challenges toward the development of non-invasive epidermal electrochemical glucose sensing systems. Recent reports claim success in glucose monitoring in human subjects using skin-worn electrochemical sensors. Such epidermal electrochemical biosensors obviate the disadvantages of minimally-invasive subcutaneous glucose biosensors and offer promise for improved glycemic control. The ability of such systems to monitor glucose non-invasively offers an attractive route toward advancing the management of diabetes and achieving improved glycemic control. However, realizing the potential diagnostic impact of these new epidermal sensing strategies would require extensive efforts toward addressing key technological challenges and establishing a reliable correlation to gold standard blood glucose meters.

1. Introduction

Diabetes is one of the most widely spread modern lifestyle diseases affecting hundreds of millions of people and ranks among the leading causes of death globally [1,2]. Frequent monitoring of blood glucose levels is essential for maintaining those levels within the physiological range and for understanding diabetes progression toward optimal management of the disease [3,4]. Considerable research efforts during the 1980s led to the introduction of self-testing blood glucose meters [5]. These devices rely primarily on different enzyme-electrode strips and have remained in widespread use by diabetes patients. However, self-testing glucose strips require inconvenient and painful blood sampling from the fingertip that compromises patient compliance and are unable to provide a high frequency of readings.

Alternatively, continuous glucose monitoring (CGM) provides detailed information unattainable by intermittent blood sampling, including real-time, “24/7” display of glucose level, rate of change of glucose level, and alerts/alarms for current or impending hypo- and hyperglycemia [6]. Such continuous monitoring provides maximal information about changing glucose levels throughout the day, including the magnitude, direction, duration, and frequency of such fluctuations, leading to improved treatment quality for people with diabetes. Efforts aimed at realizing such technology have resulted in several successful commercial subcutaneous CGM platforms. These systems commonly rely on subcutaneously implanted amperometric biosensors that measure dynamically changing glucose levels in the skin interstitial fluid (ISF), and can provide alerts to dangerous glucose levels throughout the day and night [7,8]. Such minimally-invasive sensing methods are based on the reliable correlation between glucose levels in the ISF and in blood [9,10]. Despite the demonstrated benefits of CGM, its widespread adoption has been relatively slow compared with its potential impact on glycemic control. This trend can be attributed in part to the need for frequent finger-stick validation, weekly device replacement, or potential for microbial infection [11].

Entirely non-invasive glucose sensing systems represent a highly attractive means of addressing these limitations and are thus ideal for advanced diabetes management. Major efforts over more than two decades have been devoted to developing entirely non-invasive optical and electrochemical glucose monitoring toward advanced glycemic control [12]. However, despite of this extensive activity and the tremendous appeal of non-invasive glucose sensors, realizing a reliable and stable non-invasive sensing device remains an elusive goal to date. The latter is attributed in part to unsubstantiated and misleading claims, which hampered the development of such non-invasive glucose sensors.

Herein, we review recent advances aimed at developing skin-worn non-invasive electrochemical glucose biosensors and discuss their prospects and limitations toward advanced glycemic control. The development of wearable sensors has received tremendous attention over the past decade [13–20]. Such devices are composed of flexible materials

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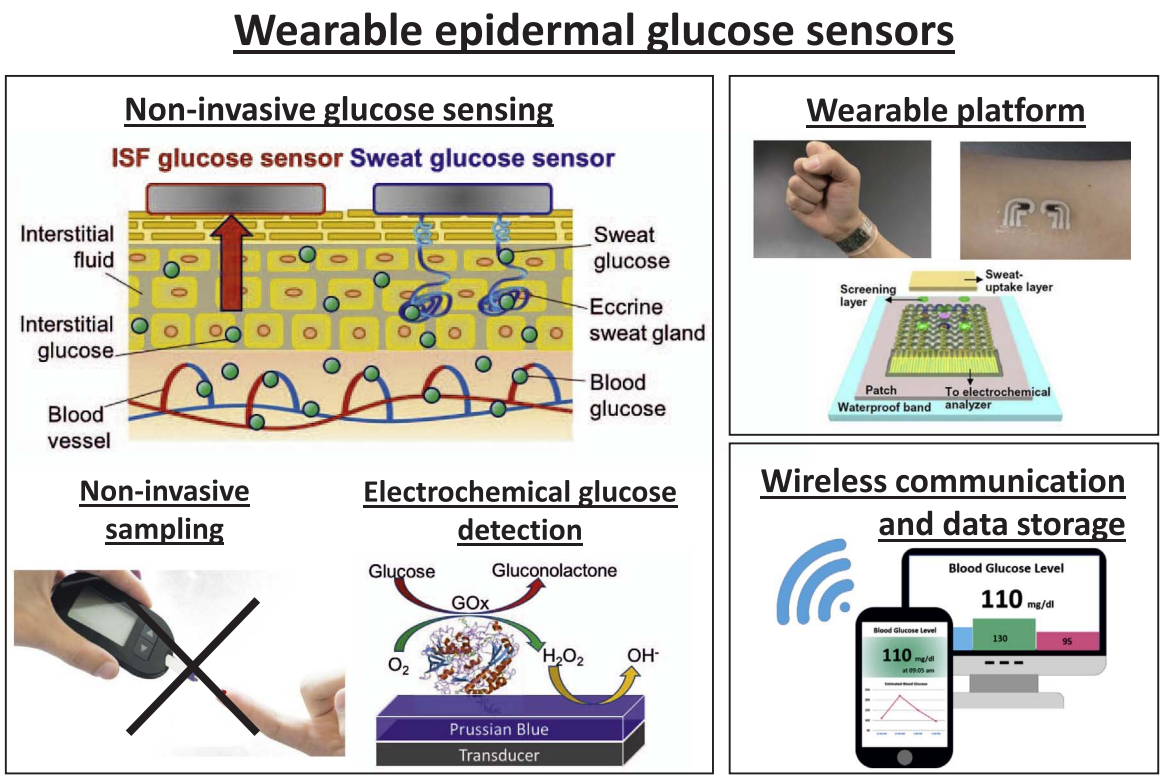

Fig. 1. Schematic diagram of wearable epidermal glucose sensors. Depiction of wearable platform from left to right reproduced from [38]. Copyright 2016, Macmillan Publishers. Reproduced from [25]. Copyright 2014, American Chemical Society. Reproduced from [41]. Copyright 2017, American Association for the Advancement of Science.

that comply with the curvilinear geometry of human skin to enable convenient, painless non-invasive monitoring. Such flexibility and conformability have been realized through the coupling of intrinsically stretchable stress-enduring materials with structures that are designed to be stretchable (*e.g.,* serpentine) [21–26]. Initial efforts in the field of wearable sensors were devoted to the monitoring of mobility and vital signs (*e.g.,* steps, heart rate, skin temperature or respiration rate). Recent activity has shifted to epidermal electrochemical monitoring of a variety of metabolites and electrolytes toward healthcare and fitness applications, [27–45], with particular recent emphasis given to non-invasive glucose monitoring.

Such non-invasive epidermal electrochemical monitoring has been investigated through utilization of two readily obtainable bio-fluids: skin ISF and sweat (Fig. 1). Glucose in these bio-fluids is diffused from glucose in blood vessels through the endothelium or sweat glands, reflecting blood glucose concentration [46]. This epidermal non-invasive (sweat, ISF) glucose sensing can be realized by fabricating body-compliant wearable platforms (such as a patch, wrist-band or temporary tattoo) and integrating wireless electronics for practical wearable application. While skin-worn glucose biosensors offer considerable promise toward the management of diabetes and improved patient outcomes, these systems yet require further development, critical evaluation and extensive validation for widespread implementation. These new epidermal electrochemical devices provide a new approach to addressing some pressing challenges in the management of diabetes. In the following sections we review the latest progress of non-invasive epidermal electrochemical glucose sensors with highlights of the design, operation, prospects and challenges of such monitoring systems.

2. Non-invasive glucose monitoring in interstitial fluid

The first commercial U.S. Food and Drug Administration (FDA) approved non-invasive glucose monitor was the GlucoWatch® biographer (Cygnus Inc.) (Fig. 2A-C). This wrist-worn system electrochemically measured glucose concentrations in skin ISF extracted by reverse iontophoresis (RI) [47–50]. Skin ISF surrounds cells and supplies nutrients through diffusion from the capillary endothelium, which leads to a reliable correlation between blood and ISF glucose levels [10]. RI is carried out by applying a mild current with two skin-worn electrodes to induce ion migration across the skin (Fig. 2C). Due to the negative charge of the skin, the flux of positively-charged sodium ions induces an electro-osmotic flow toward the cathode, which also results in the movement of the neutral glucose toward the same electrode. The GluoWatch® electrochemically detected levels of extracted ISF glucose through enzymatic glucose oxidation at skin-worn sensing electrodes modified with glucose oxidase (GO_X). The entire electrode configuration, electronic components and display were contained within a wrist-mounted watch device (Fig. 2A-B). Glucose concentrations in extracted ISF are expected to be 1000-fold more dilute relative to blood glucose. Thus, a highly sensitive glucose sensing system is required for accurate blood glucose monitoring using this method. One measurement cycle of the GlucoWatch® consisted of applying RI for 3 min followed by a 7 min detection period, allowing 6 measurements to be taken per hour over a 12 h period. The GlucoWatch® had a user-friendly interface that included an alarm for greater than 35% changes in glucose, an activity marker (for meals, exercise, and insulin injection), accompanying software for data analysis and internal memory to store up to 8500 readings [49,50]. Clinical trials of the GlucoWatch® showed adequate precision for home blood-glucose monitoring. The Cygnus GlucoWatch® was marketed in the early 2000s but was retracted from the market due to various reasons, which included reported skin irritation caused by the RI process, the long necessary warm up time (2–3 h), and the need for calibration using standard blood glucose strips. To address these drawbacks, recent research efforts have focused on producing reliable, efficient non-invasive glucose monitoring platforms.

Wang et al. recently developed a wearable, tattoo-based non-invasive glucose monitoring platform based on integrating RI with amperometric glucose detection on a flexible substrate (Fig. 2D) [25]. The iontophoretic and glucose sensing electrodes were fabricated on a single temporary tattoo platform using screen-printing, leading to a

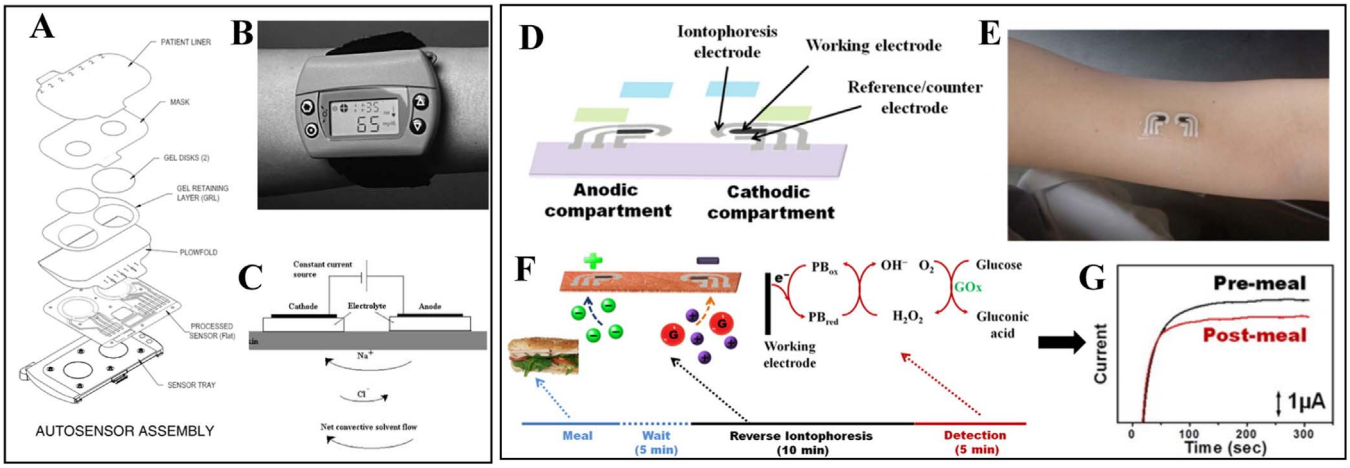

Fig. 2. Epidermal glucose sensing in skin ISF through reverse iontophoresis. A) Exploded view of GlucoWatch® biographer assembly. B) Depiction of GlucoWatch® biographer display. Reproduced with permission [50]. Copyright 2001, Elsevier. C) 'Reverse iontophoresis' process for glucose extraction. Reproduced with permission [48]. Copyright 2000, Taylor & Francis Group. D) Tattoo-based printable iontophoretic sensing configuration. E) Photograph depiction of tattoo based printable iontophoretic sensing system applied to human subject. F) Schematic representation of tattoo-based printable glucose sensing system operation. G) Tattoo-based printable glucose sensing system output on human subject before and after meal. Reproduced with permission [25]. Copyright 2014, American Chemical Society.

body-compliant and easy to wear flexible, conformal device for single use glucose measurements (Fig. 2E). This sensing platform obviated the discomfort of Glucowatch® by reducing the applied iontophoretic current for ISF extraction and by utilizing a low voltage cathodic detection of the GOx-generated hydrogen peroxide at the Prussian Blue electrode transducer (Fig. 2F). The performance of the tattoo-based electrodes was evaluated with healthy human subjects by comparing the recorded glucose signals before and after meal, and the results were validated by simultaneous blood glucose measurement using a commercial glucometer (Fig. 2G). Control experiments were carried out without enzyme modification of the glucose sensor to confirm the sensing mechanism. Although the tattoo-based device was intended for disposable use, such a sensor holds considerable promise for continuous non-invasive ISF glucose monitoring by offering a body-compliant, flexible and cost-effective platform. Future work toward the development of such systems should focus on the testing of performance over long-term use, sensor integration with wireless electronics, and examination with large populations of both healthy and diabetes-suffering individuals.

The reported tattoo-based device yet required intrusive calibration against blood glucose levels to reliably correlate measured ISF glucose readings with the concurrent glucose concentration in blood. One solution that has been suggested to realize completely non-invasive glucose monitoring is through the use of an internal standard along with RI [51]. The proposed method would utilize simultaneous sodium extraction by RI along with glucose. ISF sodium concentrations have been shown to only slightly vary in a patient throughout the day and from day-to day. Thus, measured sodium levels would only vary with the RI efficiency, which would allow calibrated glucose measurements [52]. The ratios of glucose and sodium in ISF and blood would be proportional with a determinable correlation constant (established by large population tests), and the concept could potentially be used to predict the ISF/blood glucose concentration ratio without finger-stick calibration.

Wearable ISF glucose sensors still require critical assessment during times of excessive perspiration. Throughout periods of exercise, individuals with diabetes must pay particular attention to blood glucose levels due to the increased likelihood of hypoglycemia as a result of glycemic regulation. A wearable sensor must thus be capable of distinguishing glucose signals in sweat from those in ISF in order to avoid false readings. Additionally, the RI efficiency should not be impacted by changes in skin resistance caused by enhanced perspiration. Studies have been reported on the impractical use of the GlucoWatch® during exercise, which contributed to its removal from market [53]. As the device was designed to avoid carrying out readings when high temperatures or perspiration (both led on by exercise) were detected, the resulting data points were too sparse for reliable monitoring. Sweat can also be a symptom of hypoglycemia, which would mean operation of the device ceased when it was most needed. Further, the time lag between changes in blood and ISF glucose concentrations was determined to potentially put the user in danger in terms of glycemic control [54]. Critical evaluation is thus necessary for the use of wearable ISF sensors during exercise in terms of accuracy for hypoglycemic/hyperglycemic monitoring and time lag during changes in glucose concentration.

3. Glucose monitoring in sweat

3.1. Non-invasive sweat glucose monitoring

Sweat is a very attractive bio-fluid toward non-invasive, continuous monitoring applications due to its distinct advantages, such as having the most sampling sites outside the body, continuous access, an ease of collection device placement and comfort, as well as its composition of physiologically important electrolytes and metabolites [55]. Sweat can readily be sampled at the skin surface and with small analytes, such as glucose, rapidly diffusing into sweat, fresh samples can be collected every several minutes with appropriate collection methods to give useful information for continuous monitoring. However, major challenges persist for accurate sweat glucose measurements, stemming from fluctuations in environmental parameters (*i.e.* temperature and pH variation), contamination from skin or surrounding environment, irregular sampling without iontophoretic stimulation, low production rate, and the mixing of old sample with new sweat. In terms of glucose, sweat concentrations have been shown to reliably correlate to concurrent blood glucose concentrations when properly harvested, although the partitioning pathway from blood to sweat has not yet clearly been verified [40,56–59]. Despite the good correlation, glucose monitoring in sweat is challenging due to its low concentration (~100 times dilution), which requires highly sensitive systems, particularly in the event of hypoglycemia or contamination from skin glucose residue. Moyer et al. showed a strong correlation between sweat and blood glucose concentrations in diabetic subjects, focusing on rapid sweat sampling without contamination from the skin [56]. In order to remove glucose residue, the skin surface was cleaned with soap, water, and 70% isopropanol (in water), sequentially. Subsequently, sweat was generated using iontophoretic stimulation by pilocarpine drug delivery, and collected by a perfusion method, as glucose concentrations on the skin

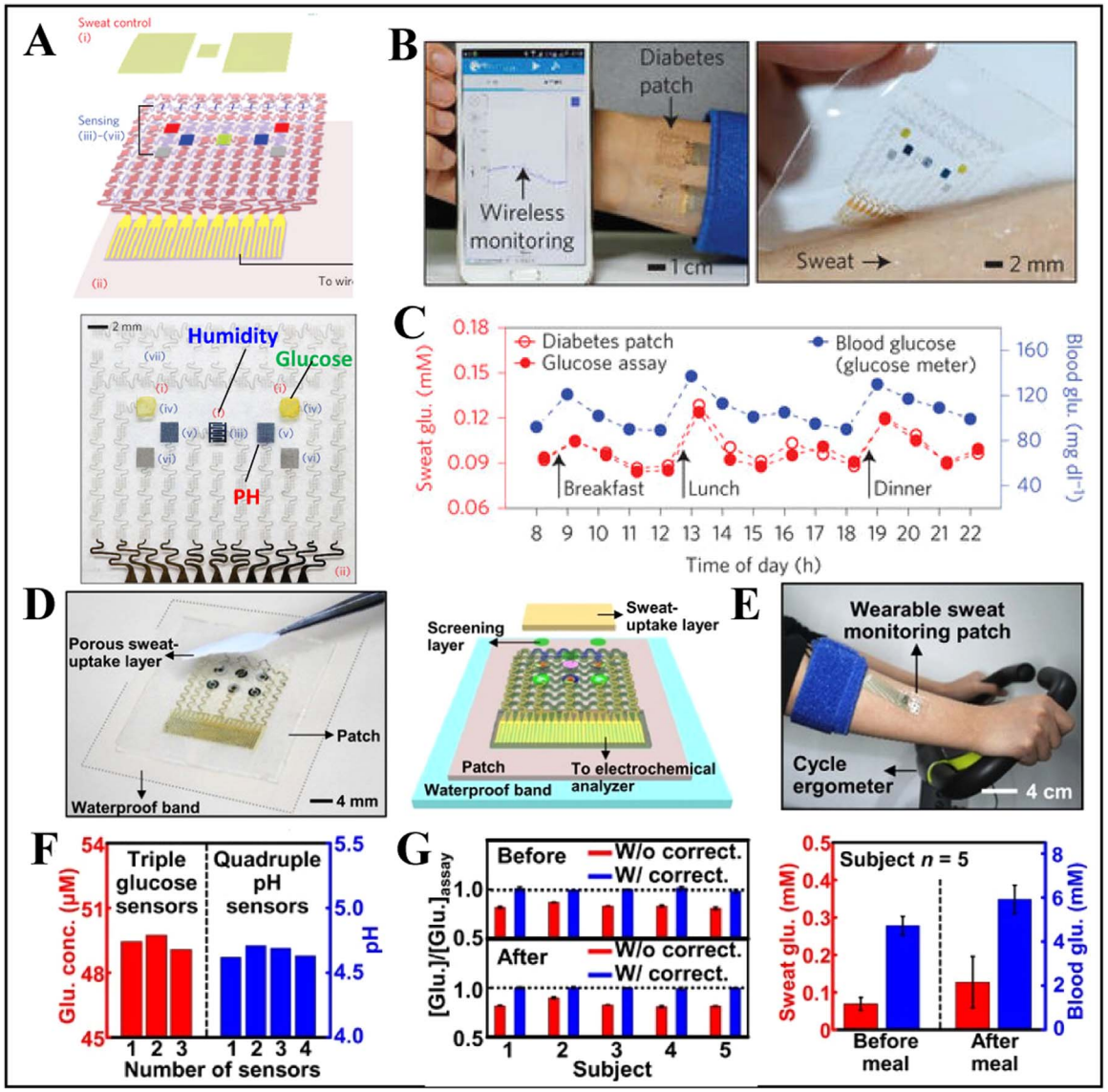

Fig. 3. Epidermal glucose monitoring with flexible patch. A) Schematic representation and photograph depiction of flexible diabetes patch composed of sweat control, multiplexed sensing and therapeutic components. B) Photograph depiction of integrated diabetes monitoring and therapy system applied to human subject. C) On-body glucose monitoring on human subject over the course of three meals with comparison to *ex vivo* and blood glucose analysis. Reproduced with permission [40]. Copyright 2016, Macmillan Publishers. D) Photograph depiction and schematic representation of wearable sweat analyte monitoring patch. E) Photograph of the subject using a cycle ergometer for sweat generation with the wearable patch on the subject's arm. F) Multimodal glucose and pH sensing to improve detection accuracy. G) Comparison of sweat glucose concentration measured using on-body sweat glucose monitoring patch and blood glucose concentration before and after meal. Reproduce with permission [41]. Copyright 2017, American Association for the Advancement of Science.

surface can disrupt accurate measurements. Such findings highlighted the need for not only sensitive detection platforms capable of continuous calibration, but also for efficient sweat collection methods without contamination from other sources on the skin's surface.

Several demonstrations of sweat glucose monitoring systems have been made on patch-type wearable platforms. In particular, the Kim group has made significant progress toward epidermal glucose sensing by incorporating a soft-material based stretchable device along with accurate measurement of glucose signal. In their initial work, Lee et al. introduced gold-doped graphene for sweat glucose monitoring and therapeutic drug delivery (Fig. 3A) [40]. The gold doping of graphene nanomaterial, prepared through chemical vapor deposition, was shown to improve electrochemical activity toward high glucose monitoring sensitivity even at low concentrations. This material was coupled with a gold mesh in a serpentine bilayer to form a stretchable, wearable device capable of precise measurement of sweat glucose with simultaneous monitoring of pH and humidity for continuous calibration (Fig. 3A). Selective glucose sensing was achieved using GO_X and Prussian Blue reactions. The efficient, on-body operation of this device was confirmed through *in vivo* testing with two healthy volunteers using exercise to generate sweat with data wirelessly transferred by a commercial handheld device (Fig. 3B). During trials, simultaneous humidity sensing was used to detect complete sweat coverage of the device and ensure accurate electrochemical measurements of both sweat pH and glucose concentration. The observed pH of collected sweat varied throughout the exercise period due to changing lactate concentrations, which could impact GO_X activity. This simultaneously monitored pH signal was used to standardize hourly measured on-body sweat glucose concentrations, which showed a suitable correlation to sweat glucose concentrations measured using a commercial glucose assay kit and blood glucose concentrations measured with a commercial glucometer over 14 h including three meals (Fig. 3C). However, with the applied hourly sampling, the incident/continuous monitoring of glucose levels and latency time between blood and sweat glucose concentrations changes could not be evaluated. This system was further utilized for microneedle-based drug delivery capable of regulating blood glucose levels in a

mouse model. Such a closed-loop monitoring and treatment system would be advantageous toward improved, continuous glycemic control in diabetes patients.

The development of this platform was continued by fabricating an ultrathin and stretchable patch-type conformal device providing efficient contact with skin for improved sweat uptake and high performance under mechanical deformation (Fig. 3D) [41]. The team introduced multiple porous sweat-uptake and water-proof layers to allow reliable sensing in as low as 1 μL volume, which was a 20 times smaller volume compared to their previous work [40]. The electrochemical signal from glucose was obtained by enzymatic reaction between GO_X and glucose and a Prussian blue transducer on porous gold. The accuracy of such glucose monitoring was maximized through multimodal glucose sensing (triplicate) combined with real-time signal correction by temperature, humidity and multimodal pH (quadruplicate) sensing. The combined sensors were worn on subjects and collected all signals including glucose during exercise. (Fig. 3E) Analysis of sweat pH variations allowed accurate monitoring of corrected glucose concentrations in five subjects with successful correlation to blood glucose shown before and after meal (Fig. 3F-G). Although these studies achieved advances in sweat glucose sensing accuracy, which was a major obstacle for practical, real-life sweat sensor applications, there yet remain several hurdles to overcome prior to reliable commercial operation including real-time signal correction with varying sweat flow rates as well as long-term stability for continuous monitoring, reproducibility between sensors and various patients, and customized wireless electronics.

Gao et al. demonstrated a flexible and fully integrated sensor array platform for multiplexed *in-situ* perspiration analysis, measuring multiple sweat metabolites (glucose and lactate) and electrolytes (sodium and potassium) as well as skin temperature in a wearable patch-type platform (Fig. 4A-B) [38]. The reported device integrated signal transduction, processing and wireless transmission for the realization of a practical wearable sensor device. The developed wearable sensor array was worn on various body parts (*e.g.*, forehead, wrist, or arms), and demonstrated the capability of real-time sweat monitoring during exercise, which resulted in varying sweat flow rates (Fig. 4C). Amperometric glucose detection was carried out through GO_X and Prussian Blue catalyzed reactions. With continued exercise, the measured sweat glucose concentration decreased. It was proposed that the increased sweat rate and duration led to dilution of sweat glucose over time, which corresponded to an observed elevation in skin temperature. The study further claimed that the increased temperature impacted the enzyme (GO_X) activity, which must be accounted for in order to avoid overestimation of actual glucose concentration. Notably, the glucose concentration measured using the flexible wearable glucose sensor correlated closely to *ex situ* measurements of collected sweat during a period of exercise (Fig. 4D). Consistent glucose profiles were observed at varying exercise intensities. However, different body parts showed differing sweat rates, which resulted in varying concentrations of analytes at any particular time due to the dilution effect, despite similar trends. Thus, the study indicated that careful assessment of sweat composition, environmental parameters and sweat rate are required for accurate monitoring of blood glucose level. Although a critical evaluation of sweat rate and its correlation with various physiological biomarkers in sweat were demonstrated, a simultaneous correlation between blood glucose and sweat glucose concentrations was not yet established. Further studies are expected to probe such correlation of sweat-blood glucose concentrations over extended periods.

Apart from sweat sampling through exercise, sweat can be stimulated on-demand using an iontophoretic drug-delivery system. The analysis of such stimulated sweat secretion is significantly more attractive for non-invasive monitoring applications not only due to the short sampling times, but also due to the ability to perform the measurements at rest. The latter could obviate risks of induced hypoglycemia in diabetic patients caused by exercise. Emaminejad et al.

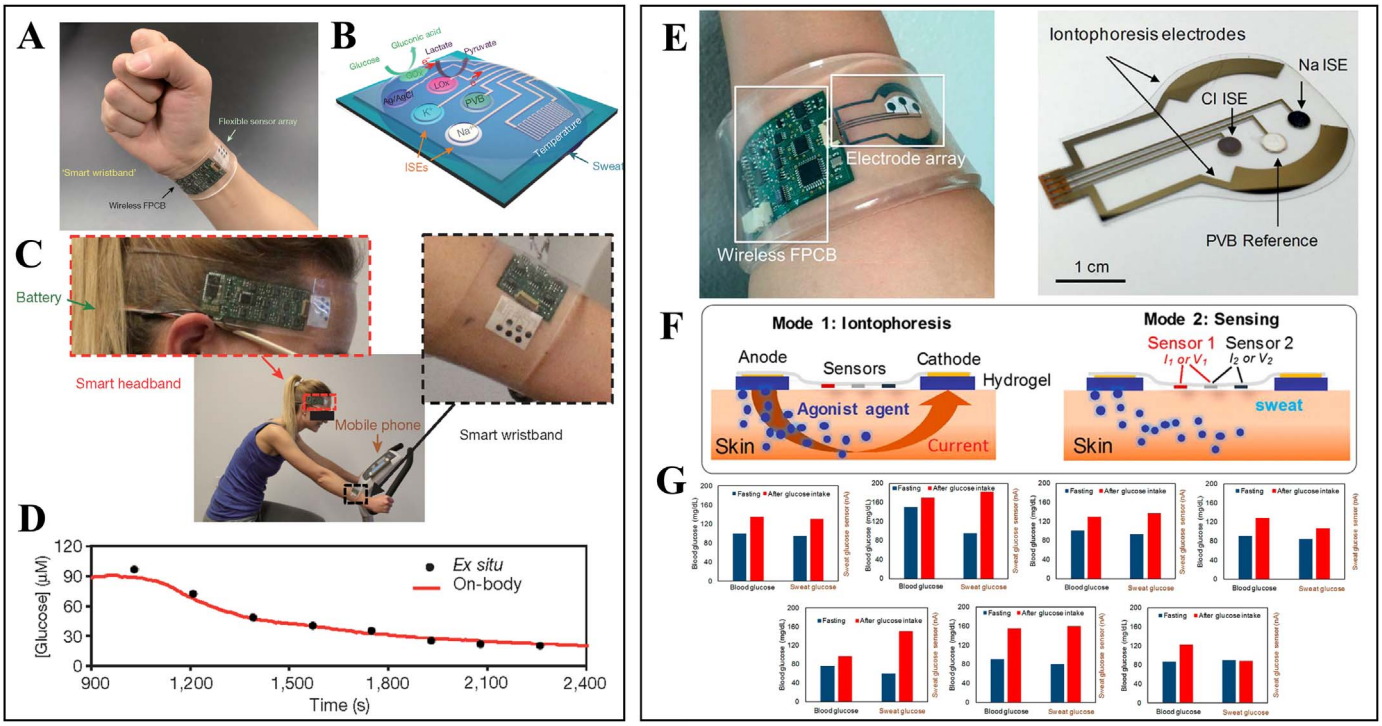

Fig. 4. Epidermal sweat glucose monitoring using a flexible sensor array. A) Photograph depiction of wearable, flexible sensor array applied to a human subject. B) Schematic representation of multiplexed, flexible sensor array. C) Photograph depictions of on-body sweat analysis using flexible sensor array with sweat generated through exercise. D) Glucose signal of on-body glucose monitoring using flexible sensor array compared to *ex situ* calibration using collected sweat. Reproduced with permission [38]. Copyright 2016, Macmillan Publishers. E) Photograph depiction of coupled autonomous sweat extraction and flexible sensing array. F) Schematic representation of iontophoresis and sensing mode operation for autonomous sweat extraction and multiplexed, flexible sensing array. G) Comparison of on-body sweat glucose and blood glucose analysis in human subjects before and after meal. Reproduced with permission [60]. Copyright 2017, National Academy of Sciences.

described the integration of an iontophoretic sweat stimulation system with an electrochemical glucose sensing system on a single, wearable platform (Fig. 4E) [60]. Sweat inducing drugs (*i.e.* pilocarpine, acetylcholine, and methacholine) were delivered by forward iontophoresis, utilizing charge repulsion between the positively-charged drug molecules and the anodic iontophoretic electrode (Fig. 4F). Glucose concentrations in the induced sweat were measured using an amperometric glucose sensor through GO_X and Prussian Blue reactions. This device was originally developed to measure Na^+ and Cl^- concentrations toward cystic fibrosis diagnoses but was readily extended to glucose monitoring. The glucose sensing performance was evaluated through off-body measurements using the collected sweat from healthy human subjects by comparing measured glucose concentrations before and after glucose intake with simultaneous measurements of blood glucose using a commercially available glucometer. Among seven subjects, six showed an increased sweat glucose signal with correlated blood glucose increase (Fig. 4G). These results were very promising toward non-invasive glucose monitoring using a epidermal sensor platform without the need for strenuous sweat generation by exercise. Future activity in this direction should include demonstration with on-body measurements for practical monitoring scenarios, along with additional validation and control experiments. These large-scale studies will assess the potential of this sweat production method for reliable glucose sensing applications and establish the correlation of its data with blood glucose concentrations.

Alternative designs to epidermal patch type sensors have also been presented for wearable sensing applications. Sempionatto et al. presented a fully integrated, multiplexed sweat chemical sensing eyeglasses platform for lactate, glucose and electrolyte monitoring [42]. This wearable system proved capable of simultaneous, continuous monitoring but lacked verification with necessary control experiments as well as correlation to concurrent blood glucose levels.

A detailed comparison of the different devices discussed in this review is summarized in Table 1. This Table compares the capabilities of the wearable epidermal glucose sensing technologies and highlights remaining challenges toward widespread practical applications. Such future prospects and challenges are discussed in the following section.

4. Conclusions: prospects and challenges

We have reviewed recent advances toward the development of non-invasive epidermal electrochemical glucose sensing systems. The new epidermal electrochemical biosensors could provide continuous, “24/7”, real-time glucose monitoring, which can encourage patient self-monitoring and address limitations of subcutaneous, minimally-invasive glucose biosensors (*e.g.*, frequent finger-stick validation, surface fouling, frequent replacement or microbial infection). Such epidermal glucose sensing systems have been realized by monitoring ISF or sweat glucose, demonstrating a correlation with blood glucose levels and integration on body-compliant wearable platforms. Key advances toward successful implementation of such devices were made through the use of cost effective fabrication techniques (such as screen printing), system integration in body-compliant wearable platforms (by soft material based flexible, stretchable designs), improved accuracy of measured glucose signal, demonstration of correlation with blood glucose level, and stimulation/control of non-invasive bio-fluids collection. Such recent progress toward non-invasive epidermal glucose monitoring offers an inspiration and promising opportunities in advancing glycemic control.

The development of epidermal electrochemical glucose biosensors for diabetes management is just beginning. Despite promising recent advances, there remains numerous challenges to overcome for the successful implementation of non-invasive epidermal glucose monitoring platforms, combining accurate real-time glucose readings with long-term stability. In particular, large-scale studies are required to critically assess the accuracy and reliability of these devices toward improving glycemic control in individuals with diabetes. Significant improvements and extensive validations are thus necessary prior to the realization of clinically useful epidermal glucose monitoring systems. Challenges for epidermal glucose monitoring using skin ISF, other than skin-irritation from RI, stem from interference from other glucose sources (such as sweat glucose during exercise, and glucose residue on skin), and inconsistent ISF extraction efficiency through RI. Although sweat is a very useful non-invasive bio-fluid for glucose monitoring, difficulties in constant and fresh sweat sampling (without any contamination) remain a key barrier for achieving reliable sweat and blood glucose correlations. A reliable means of efficient, selective fresh glucose uptake is crucial to the development of sweat-based monitoring

Table 1
Summary of epidermal wearable glucose sensors.

Wearable glucose sensor	Biofluid	Sampling method	Advantages	Next Steps	Refs
GlucoWatch® biographer	ISF	Reverse iontophoresis	• FDA approved • First commercialized product of this type • Continuous monitoring • Electronics for measurement and data storage were combined	• Minimize skin irritation • Shorter warming up period • Interference by sweat generation • Time lag compared to blood glucose	[50]
Temporary tattoo	ISF	Reverse iontophoresis	• Cost effective • Easy to wear • No skin irritation	• Single use • Study stability and reproducibility towards continuous use	[25]
Multiplexed wearable, flexible array patch	Sweat	Exercise	• Simultaneous multiplexed sweat sensing • Integration of customized wireless electronics • Extensive characterization of sweat	• Establish correlation to blood glucose • Large-scale validation	[38]
Sensor array patch coupled with induced sweating	Sweat	Iontophoresis (Stimulated)	• Integration of iontophoretic sweat generation with glucose sensing • Integration of customized wireless electronics	• Extension to on-body monitoring	[60]
Graphene- based stretchable patch	Sweat	Exercise	• Accurate monitoring by combination of pH, temperature, and humidity • Nanomaterials-based sensitive glucose sensor • Soft materials incorporated for stretchable/flexible device	• Increase the sampling frequency • Replacement of the commercial analyzer with conformal interface • Large-scale validation	[40]
Wearable patch, multimodal glucose sensor	Sweat	Exercise	• Controlled sweat uptake • Improved accuracy of glucose sensing (multimodal sensing array) and correction with sweat pH value	• Demonstrate continuous monitoring • Replacement of the commercial analyzer with conformal interface	[41]
Eyeglasses sensor	Sweat	Exercise	• Real-time continuous monitoring of sweat glucose • Integration with customized wireless electronics	• Detailed study and validation • Temperature/pH compensation	[42]

systems [56]. Further efforts should focus on accurate epidermal glucose measurements by combination with sensing of other physiological parameters (pH, temperature, humidity) toward continuous calibration and improved accuracy and correlation with blood glucose level. Future efforts should also aim at simultaneous monitoring of additional diabetes-related markers toward a more comprehensive array of information regarding real-time glucose metabolism. Further improvement in iontophoretic sweat stimulation is desired for controllable (consistent and reproducible) sweat generation without the need for exercise. Additional work should also focus on improved sweat collection, flow and replenishment in connection to epidermal flexible microfluidic devices. Overcoming these and other challenges will be crucial for the advancement of continuous epidermal glucose monitoring to realize its potential impact.

In order for any calibration-free, non-invasive epidermal glucose monitoring devices to achieve widespread application, special attention should be given to detailed validation for establishing their response to changing blood glucose levels, achieving sensing consistency between individuals, long-term stability and day-to-day sensing reliability through examination in large population studies. Further, understanding the time lag between changes in blood glucose concentrations and those monitored by these epidermal devices must be found to prevent dangerous hypo- or hyperglycemia conditions. To achieve the targeted goals, a thorough understanding of all components of the epidermal monitoring systems is required, including the applied biochemical sensing mechanisms, skin physiology, device surface and material chemistries, and sensing electrochemistry as well as the interface of these systems. The successful realization of epidermal glucose monitoring platforms requires not only consideration of these scientific problems, but also economic, legal and commercial concerns with patient and physician education of key importance. We envision that through a combination of these technological advances with large scale studies, glucose concentrations can be reliably and non-invasively monitored with minimal discomfort to patients for widespread applications toward improved glycemic control and autonomous therapeutic interventions through integration with autonomous, closed-loop insulin delivery systems. Given the rapid recent progress, it seems that epidermal glucose monitoring has only scratched the surface of its full diagnostic potential and is poised to significantly increase its impact on medicine.

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