Bio-Design and Manufacturing (2022) 5:9–13
https://doi.org/10.1007/s42242-021-00176-x

PERSPECTIVE

Minimally invasive technology for continuous glucose monitoring

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Received: 14 October 2021 / Accepted: 17 November 2021 / Published online: 14 January 2022

Introduction

Despite the numerous breakthroughs made in medical and biomedical technologies, biosensing underneath the skin without any associated pain still sounds like a dream yet to be realized.

Minimally invasive biosensors refer to functional or electronic sensors that can contact the interior environment of living organisms and their biological tissues, while the connected bulk devices remain on the surface of the biological objects [1]. Minimally invasive biosensors are currently a key research area because they can not only meet the increasing technical demands to precisely detect biological activities inside biological objects, but also provide an ideal platform to externally incorporate complicated functionalities and electronic integration [2]. The current development level of minimally invasive sensing still necessitates solving the constraints and bottlenecks in the three aspects of functionalities, sensitivity and biocompatibility [3]. In this perspective, we select minimally invasive sensors as a representative research object with the aim to solve the limitations of current diabetes diagnosis and treatment approaches.

Diabetes, a major clinical chronic disease, seriously affects national health together with social and economic stability [4]. At present, after cardiovascular and cerebrovascular diseases and malignant tumors, diabetes has become the third most prominent disease affecting human health in the developed world, both in the physical and mental aspects. What is more, while obesity has turned into a global problem in recent years, the incidence of diabetes is rising rapidly in modern populations, driven by rapid urbanization and unhealthy eating habits together with increasingly sedentary lifestyles [5, 6]. Statistics from the International Diabetes Federation (IDF) for 2019 show that the number of adults with diabetes reached 463 million globally, and the prevalence rate of this condition was as high as 9.3%. This number is expected to reach 578 million in 2030 and up to 700 million in 2045 [7]. Diabetics need the injection of appropriate amounts of timely insulin according to blood glucose monitoring results, so as to maintain the systemic blood glucose homeostasis in daily life. The measurement of blood glucose and medical treatment need to be frequently performed, i.e., 3–8 times every day [8, 9]. Currently, the conventional blood glucose monitoring methods used in clinics mainly comprise sampling blood from the fingertips or a vein, which is then placed on a glucometer or a glucose test paper for glucose measurements. At the same time, diabetes is likely to cause various complications such as lower limb ischemia, foot ulcers, skin ulcers and infections [10, 11]. The detection of several physiological indicators of the microenvironment of diabetic tissue is essential to understand the physiological mechanism of the diabetic milieu and guide treatments for diabetic complications. For example, pH, lactic acid and uric acid are usually related to diabetic acidosis and diabetes-induced local limb ischemia [12], while reactive oxygen species are associated with inflammation caused by diabetes. Clinically, the accurate detection of these physiological indicators mainly relies on frequent, invasive and painful blood sample tests that bring inconvenience to patients, increasing the risk of wound infection and reducing treatment compliance [13]. Moreover, blood sampling detection approaches can only obtain instant and isolated data of biological indicators for a time span of one day, which makes them unable to continuously monitor the important indicators in the long term. The above shortcomings limit the in-depth applications of tracking the fluctuation of diabetes indicators, deciphering the disease details and guiding clinical treatment. Therefore, the existing diabetes diagnosis and treatment technologies need to

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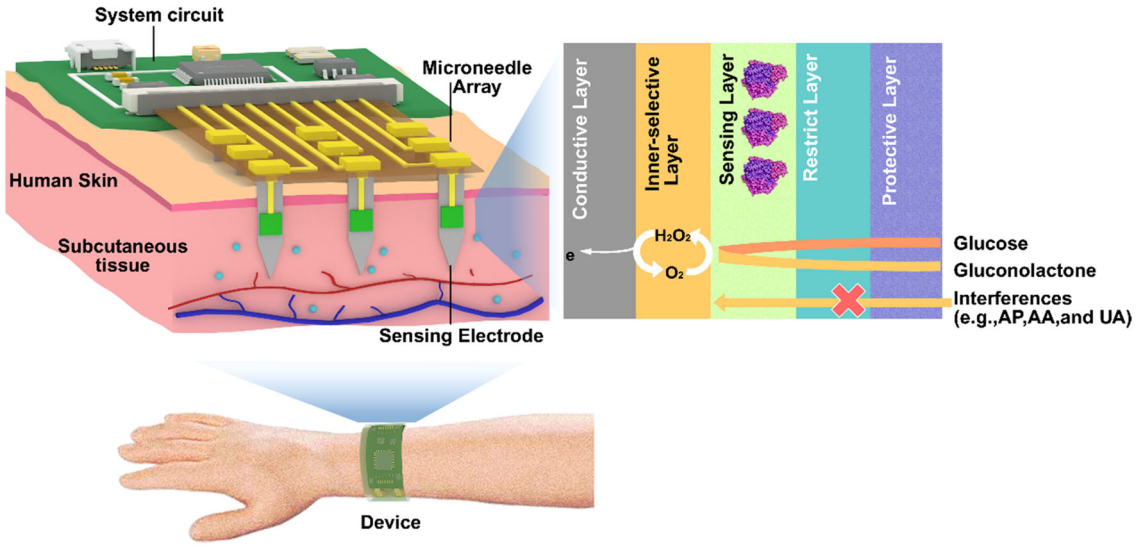

Fig. 1 Schematic of MN-based smart device for continuous blood glucose sensing

urgently fulfill the following criteria: (1) accurate detection of blood glucose, which should meet the clinical standard errors < 15%; (2) continuous monitoring of blood glucose levels together with real-time feedback, intelligent and controlled drug delivery; (3) biosafety or harmlessness to the human body (biocompatibility); and (4) synchronous detection of biological indicators related to diabetes in order to reveal the mechanisms of diabetes development and promptly adjust the treatment plan.

In recent years, significant progress has been made in the field of dynamic blood glucose monitoring based on minimally invasive electrodes [14–16]. Blood glucose electrodes are placed in the subcutaneous tissue fluid of patients to realize the continuous (every 5–30 min) detection of glucose concentration in the interstitial fluid (ISF). Since the exchange of substances between subcutaneous capillaries and ISF takes place continuously, the glucose concentration in ISF can be converted to blood glucose level [17, 18]. In addition, continuous blood glucose monitoring can be used as an electrical signal sensing device in conjunction with an insulin pump, which is a promising strategy to develop an intelligent closed-loop theragnostic device. However, the accuracy of a continuous blood glucose monitoring system is reduced due to subcutaneous inflammation and tissue fibrosis caused by the implanted electrodes, which have a length of several millimeters. Standard implantable electrodes also carry the risks of pain, bleeding and infection, which can lead to decreased comfort, accuracy and compliance over the long term [19]. In view of the shortcomings of existing blood glucose monitoring approaches for diabetes, noninvasive or minimally invasive blood glucose monitoring based on new materials and technologies has become a hot spot in both academia and industry in the past few years [20–22]. Researchers have proposed a variety of novel noninvasive sensing technologies, such as near-infrared spectroscopy detection, tear detection, salivary detection, sweat detection and reverse iontophoresis-based detection. Regrettably, the glucose concentration in biological fluids such as tears, saliva and sweat is much lower than that in ISF and blood, resulting in a large deviation in the response to fluctuations in the actual blood glucose level. Moreover, the accuracy of noninvasive methods based on optical detection and reverse iontophoresis-based detection is still lower than the required clinical standards; hence, these technologies have not yet obtained clinical approval.

Promisingly, with the promotion of advanced micro-/nano-manufacturing technologies, such as micro-/nano-processing and laser microprocessing, cutting-edge painless transdermal technology based on microneedle (MN) arrays is gradually emerging. The length range of MN is usually 500–800 μm, which can just penetrate the stratum corneum of the skin and touch the dermis without reaching the blood vessels or nerves inside the dermis [23, 24]. The minimally invasive characteristics of MNs can avoid not only the pain caused by transdermal behavior, but also tissue inflammation and fibrosis caused by tissue trauma [25], as shown in Fig. 1. Aimed at the high-sensitivity, safe and simultaneous detection of multiple subcutaneous biological indicators in the subcutaneous microenvironment of diabetes, researchers nowadays are increasingly focused on whether it is possible to develop a minimally invasive transdermal sensing technology based on MN arrays [26–28]. This highlights the dynamic change process of various physiological indicators of the subcutaneous microenvironment of diabetes complications.

Recent advancements

The recent emergence of material science greatly encouraged the development of minimally invasive electrodes for glucose monitoring. For example, Xie et al. proposed an implantable sensor with zwitterionic polymer coating to reduce signal noise [29]. It was shown that such polymer-coated sensors could accurately record glucose levels without recalibration. Peng's laboratory developed a multi-ply sensing fiber-based implantable sensor [30], which could realize the simultaneous detection of multiple biomarkers in real time, including ions, prostate-specific antigens, H_2O_2 and glucose. A single-ply sensing fiber bundle was fabricated by twisting carbon nanotubes into a helical bundle resembling muscle filaments and then further modified with corresponding sensing components. By twisting several single-ply sensing fibers with different sensing components together, the multi-ply sensing fiber-based sensors were obtained. According to the in vivo experiments therein, the sensors realized the real-time monitoring of H_2O_2 in tumors of mice. Furthermore, Ca^{2+} and glucose concentrations in the blood vessels of cats could be detected for 28 d. Although both polymer-coated sensors and fiber-based multiplexed sensors are implantable sensors with tiny structures, they are not MN array-based transdermal sensing electrodes. Inspired by these findings, a number of studies have paid particular attention to the development of MN-based sensing platforms in subsequent research.

Besides the success of implantable electrodes, MN-based sensors have recently emerged as promising tool for new-generation in vivo glucose detectors. Remarkably, Voelcker et al. reported a high-density MN array-based sensing system for the electrochemical detection of glucose [31]. This glucose sensing patch is a three-electrode system including a working electrode (W.E), a reference electrode (R.E) and a counter electrode (C.E), where each electrode is constructed by an independent Si MN array. After the corresponding functionalized modifications, three MN array-based electrodes are assembled into an integrated glucose sensing patch, which can pierce the skin and contact the ISF in a minimally invasive manner. The in vitro electrochemical measurements showed that the MN glucose sensing patch possessed a high sensitivity of 0.1622 $\mu A\ mM^{-1}\ cm^{-2}$, a low detection limit of 0.66 mM and good selectivity. Moreover, it exhibited a high capacity to monitor ISF glucose changes in situ, and its acquired data showed a close correlation with the blood glucose levels measured by a commercial glucometer. Hence, this work provided an MN-based transdermal diagnostic tool to facilitate the direct monitoring of glucose level in a painless procedure.

Li et al. presented an integrated closed-loop system based on mesoporous MN array for diabetes diagnosis and treatment [32]. As the main component of this system, the glucose sensor consists of a mesoporous MN array, a planar glucose electrode, a reverse iontophoresis extraction component and a 3D-printed sensing chamber. After the mesoporous MNs pierce the skin, the glucose in ISF will be extracted into the chamber via reverse iontophoresis, followed by detection via the planar electrode. The in vitro detection of the glucose sensor showed a detection sensitivity of 54.2 nA mM^{-1} and sensing linear region of 0–20 mM, which can meet diabetic applications. The in situ and real-time monitoring revealed that this MN-based glucose sensor can record blood glucose fluctuations similar to those determined by a glucometer, where the average errors were about 10.4% and 12.9% of healthy rats and diabetic rats, respectively. The sensing error of about 90% of data was below 20%, which well satisfies the clinical error threshold of < 15%. Apart from tracking glucose fluctuations, the overall theragnostic system can also release insulin to regulate hyperglycemia in a timely and intelligent manner, which makes it a promising platform to improve the treatment efficiency of diabetic patients.

Difficulties and challenges

In spite of the recent successes, the following difficulties need to be solved to realize this technology:

1. Existing minimally invasive sensors have usually focused on the design of MN-based transdermal sensing of single analytes, which lack the ability to simultaneously detect multiple analytes within the same platform. Limited by the manufacturing precision of 3D MNs and the complex technological process of fabricating different electrodes, a 3D MN array with a single needle as an independent sensing electrode has not been realized; the fabrication of independent electrodes on tiny tips of MNs using micromachining methods remains a considerable challenge.
2. Existing electrochemical enzyme electrodes generally rely on the synthetic materials of inorganic/organic electron mediators; thus, the highly sensitive "enzyme—electrode" electron transfer has not yet been achieved. Classic glucose electrodes, for example, are based on the forms of "first generation" or "second generation," where the redox center is wrapped inside the enzyme molecule and is too far away from the electrode surface to achieve the rapid enough transfer of electrons. Thus, such electrodes usually require electron mediators to facilitate the electron transfer between enzyme and electrodes, such as H_2O_2, ferrocene, synthetic polymers or nano-materials. However, such methods are not only easily limited in detection specificity and linear range, but also pose great challenges to manufacture large-scale electrodes. Therefore, the development of "third-generation" electrodes with direct enzyme connection is an important direction to realize the direct electron transfer between enzyme and electrodes.

3. The surface biocompatibility of minimally invasive electrodes has not been effectively solved. Implanted electrodes frequently lead to injury and subcutaneous rejection, which activates various inflammatory factors and reduces the detection accuracy. Synthetic materials such as electronic mediators may also induce inflammatory reactions and tissue fibrosis, affecting the stability of electrodes and limiting the feasibility of clinical application. Many commercially available electrodes require patients to take a daily blood sample for signal calibration, and replace the implanted electrodes every 1–2 weeks. Although some research groups have recently proposed polymer coating or anti-inflammatory drugs to improve the biocompatibility of implanted electrodes, these strategies are also prone to interfere with the electrochemical performance of enzyme electrodes. In conclusion, it is extremely challenging to solve the above limitations, including structural design, material preparation and electrode performance.

The continuous glucose monitoring industry possesses the characteristics of large market space, high technological barrier and excellent commercial track. Currently, only four companies, including Dexcom, Abbott, Medtronic and Senseonics, have obtained Food and Drug Administration (FDA) approvals for continuous glucose monitoring technologies, indicating the existence of the high technology barrier. By helping diabetic patients to keep track of their blood glucose changes during exercise, diet, hypoglycemic treatments and other daily activities, continuous blood glucose monitoring systems can contribute to the overall improvement diabetic patients' life quality. Thanks to the information of blood glucose change trend, early warning signs of high/low blood glucose and the prediction of blood glucose level change provided by the continuous glucose monitoring system (CGMS), it can help patients avoid inaccurate insulin injections due to the incomplete information from a digital blood glucose meter. In view of the problems of traditional glucose meters, CGMS is suitable for type 1 diabetes patients and type 2 diabetes patients requiring intensive insulin treatments. Furthermore, it supplies users with comprehensive and continuous glucose information, guiding them to reduce the blood glucose fluctuation level, thus preventing the occurrence of hypoglycemia, which is in line with the modern diabetes management concepts.

As a new type of transdermal sensing technology, MN array has gained wide interest in the field of continuous glucose monitoring in both academia and industry. With the rapid development of MN array micromachining, electronic medium material preparation and biocompatible coating technologies, the application of MN array in the real world and in clinics has a promising future, will hopefully lead to new intelligent solutions for the treatment of diabetes and may be extended to wearable monitoring applications for other chronic diseases.

Acknowledgements The authors would like to acknowledge financial support from the National Natural Science Foundation of China (Nos. 61771498, 61901535 and 81970778), Science and Technology Planning Project of Guangdong Province for Industrial Applications (No. 2017B090917001), Guangdong Province Key Area R&D Program (No. 2018B030332001), Science and Technology Program of Guangzhou, China (No. 202102080192), Guangdong Basic and Applied Basic Research Foundation (Nos. 2021A1515012261, 2019A1515012087, 2020A1515010987 and 2020A1515110424) and Key Program of Sun Yat-Sen University (No. 20lgzd14).

Author contributions XX conceived and supervised the study. XH and JY contributed to methodology and completed the original manuscript. SH and HC investigated the study. All authors contributed to writing review and editing.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study does not contain any studies with human or animal subjects performed by any of the authors.

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