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Revisiting the use of biological fluids for noninvasive glucose detection

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“To improve the accuracy, specificity and convenience of detection, biosensors for blood glucose monitoring are being developed based on non-blood biological fluids, such as sweat, tears, urine and saliva with the aim of achieving noninvasive, real-time glucose monitoring for diabetics.”

First draft submitted: 19 January 2020; Accepted for publication: 5 February 2020; Published online: 17 March 2020

Keywords: biosensors • diabetes • DNA sensor • plasma • protein sensor • saliva • sweat • tears • urine

Glucose monitoring is critical for controlling blood glucose levels and alleviating symptoms in hyperglycemia and diabetic patients. Diabetes mellitus is a metabolic disease resulting from defects in islet insulin secretion and insulin resistance, leading to abnormalities in metabolism and diseases [1]. Hyperglycemia and hyperlipidemia are two primary clinical features of diabetes [2]. Uncontrolled diabetes is associated with serious complications, including nephropathy, retinopathy, limb ulcers and cardiovascular disease [3]. In particular elderly patients, with diabetes, often present poor conditions due to an inability to manage and modulate diabetes with declining health and/or cognitive ability. Although there is no established cure or medical prophylaxis for diabetes, symptoms can be relieved and complications can be alleviated with the use of appropriate medications. The primary goal of diabetes treatments, which may include insulin injections and oral hypoglycemic and glucose-lowering drugs, is to maintain blood glucose within normal levels [4]. In this sense, regular blood glucose monitoring is important for effective management of diabetes and optimal treatment outcomes.

Traditional blood glucose testing is a standard practice and its results are used as a marker for various diseases. Glucose monitoring with finger stick involves the use of an enzyme-based test strip at specified time intervals [5]. However, it is associated with physical pain and infection risk, especially when pricking is performed daily and by the elderly on a regular basis [6]. There are newly developed glucose biosensors, such as subcutaneous amperometric electrodes and microdialysis [7] that provide a relatively fast response over a dynamic range, but still require fingertip piercing as well as providing a delayed reading. Although this technology has yielded improved accuracy relative to blood-alternative methods, their inability to provide noninvasive, real-time testing has limited their development [8].

Various types of biosensors have been developed including enzymatic and nonenzymatic electrochemical glucose sensors, spectroscopic methods, infrared spectroscopy and surface plasmon resonance [3]. Unfortunately, spectral signal-to-noise levels caused by skin thickness has limited the sensitivity and accuracy of these blood glucose measurement methods [6]. Additionally, the safety and cost of these methods have hindered their daily use. To improve the accuracy, specificity and convenience of detection, biosensors for blood glucose monitoring are being developed based on non-blood biological fluids, such as sweat, tears, urine and saliva with the aim of achieving noninvasive, real-time glucose monitoring for diabetics.

Among these biofluids, sweat is an accessible thermoregulating biofluid that contains diverse electrolytes and hormones with the potential to be utilized for monitoring of health status and detection of diagnostic signs of disease [3]. Analytes in sweat have been related to blood concentrations and thus can be used to provide a blood glucose index. Multi-electrode sweat sensors represent a convenient, noninvasive alternative to traditional finger-pricking approaches that can provide continuous monitoring and real-time feedback [9]. The development of a wearable, disposable sweat-based device for measuring blood glucose levels by electrochemical analysis of sweat on the skin has been reported. In this case, drugs can be loaded on to temperature-responsive phase change

nanoparticles within a hyaluronic acid hydrogel for transdermal delivery via a microneedle in response to the patient's glucose level [10]. This dynamic responsive-sensor design can provide noninvasive glucose monitoring together with precisely controlled drug release as a form of feedback-guided therapy [10]. Meanwhile, a sensor, called Continuous Lifestyle Awareness through Sweat Platform, has been recently developed [11]. The Continuous Lifestyle Awareness through Sweat Platform combines electrochemical impedance spectroscopy with a chronoamperometry technique to track alcohol and glucose fluctuations in real-time based on current changes at the electrode–sweat interface. This approach utilizes rapid, dynamic monitoring of minute quantities of perspired sweat and can be adapted easily for alcohol and glucose detection; this is particularly useful in some cases given that ethanol consumption increases diabetes risk [11]. The development of sweat-based detection has been limited to some extent by biological factors. Glucose concentrations in sweat are much lower than in blood and daily sweat collection can be quite difficult, especially for elderly patients. In addition, measurement accuracy can be compromised by glucose oxidase activity caused by changes in pH, contamination of the skin surface, environmental temperature and mechanical friction on the skin surface [10].

Human tears are an extracellular fluid containing organic molecules, such as proteins, glucose and electrolytes, that surround ocular tissues. The biomolecular characteristics of tears can reflect physiological conditions and one's health status [12]. Tear fluid is being considered for glucose monitoring owing to an empirically demonstrated correlation between tear glucose (TG) and blood glucose [13]. In this regard, the TOUCH TG sensor for noninvasive TG detection was developed. The sensor collects tear fluid in a soft foam plug and transfers it to a sensing well where TG is detected electrochemically [14]. The TOUCH TG sensor is a highly specific and accurate glucose detector that can produce results within 10 s from a very small tear sample. Thus, in addition to being safe and noninvasive, the TOUCH TG sensor improves measurement convenience. In addition to their primary application in vision correction, contact lenses can serve as a biosensing platform to monitor glucose levels in the ocular humor. Lin *et al.* reported a nonenzyme phenylboronic acid-based hydroxyethyl methacrylate contact lens that swells as it absorbs glucose and increases in thickness in response to increasing glucose concentrations [15]. The lens can be photographed with a smartphone and subjected to lens change-in-thickness assessments in a smartphone application. In this way, phenylboronic acid-based lenses have the potential to provide continuous and noninvasive monitoring of glucose, saving patients time relative to other portable diagnostic tools [15]. Nevertheless, there are challenges associated with TG measurements to be resolved. Tear collection methods involving mechanical or chemical stimulation can result in conjunctival damage, discomfort and, potentially, consequent alterations in TG concentration [14]. Blinking can cause movement artefacts in the sensor signal [3]. Additionally, some patients are not comfortable with wearing contact lenses, especially among elderly patients needing daily monitoring.

Saliva is an informative fluid containing a large number of analytes that reflect one's physiology and health status [16]. Because saliva glucose levels correlate directly with blood glucose levels [6], salivary glucose can be utilized as a diagnostic resource for the identification of biomarkers of oral and systemic diseases [16]. Soni *et al.* developed a noninvasive optical sensor with immobilized glucose oxidase and pH-responsive pigment on filter paper, wherein the filter paper can be subject to color changes when its chemoreactive band reacts with glucose in saliva, and those color changes can be detected with a smartphone camera and application [17]. However, differences among smartphone models, camera pixels and ambient light may affect the application's output. Of great interest in this context is the recent development of a highly sensitive and selective flexible biosensor called the organic electrochemical transistor (OECT) [18]. In saliva, the OECT has a low detection limit of 30 nM and a rapid detection time of a few tens of seconds. The OECT platform converts the detection of biochemical molecules into electric currents such that glucose levels can be read out on a mobile phone being used as portable professional equipment or for home use. To improve its specificity, the OECT has an enzyme coating to prevent interference in saliva; OECTs with a glucose oxidase enzyme coating have been shown to have selective glucose sensitivity [18]. The biosensor can be mass produced with high reproducibility at a low cost (HK\$3–5) with an inkjet printer, making it an inexpensive saliva glucose meter candidate for daily use by elderly patients, including at risk of developing diabetes. Against this background, early diagnosis of cancer is critical for cancer research and thus multiplex cancer biomarkers, such as proteins, nucleic acids and microRNA, are the promising target for noninvasive detection using a highly sensitive and specific biosensor, OECT, despite their expression levels being very low in biofluids [19]. In this sense, a novel optoelectronic microfluidic sensor has been previously developed for the diagnosis of early detection of stomach cancer by means of using dissolved CO₂ and NH₃ in saliva that could distinguish the saliva of the healthy person from patients [20].

There is great potential for the development of noninvasive approaches to monitoring glucose levels via biological fluids with having desirable properties of portability, accuracy, low-cost, ease-of-use and convenience. In this regard, saliva is a biological fluid with noteworthy advantages for health monitoring owing to its ease of collection and minimal discomfort, and thus suitability for home use. The development of cost-effective, highly sensitive and specific diagnostic glucose measurement tools can benefit elderly prediabetic and diabetic populations greatly. More interestingly, the use of biofluid has potential in the detection for the early diagnosis of cancer and diabetes, making them an attractive alternative to traditional means of detection. Future investigations into the use of biological fluids for non-invasive glucose detection may open up new avenues for the multiplex biomarker detection for the early diagnosis of various diseases, including diabetes and cancer with transistor arrays integrated in microfluidic systems in the near future.

Financial & competing interests disclosure

The work described in this paper was supported by the Innovation and Technology Fund, ITC Commission of the Government of the Hong Kong Special Administrative Region, China (ref. no.: MRP/040/18X). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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