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James Lind Alliance Research Priorities

Is it possible to constantly and accurately monitor blood sugar levels, in people with Type 1 diabetes, with a discrete device (non-invasive or invasive)?

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Abstract

Real-time continuous glucose monitors using subcutaneous needle-type sensors continue to develop. The limitations of currently available systems, however, include time lag behind changes in blood glucose, the invasive nature of such systems, and in some cases, their accuracy. Non-invasive techniques have been developed, but, to date, no commercial device has been successful. A key research priority for people with Type 1 diabetes identified by the James Lind Alliance was to identify ways of monitoring blood glucose constantly and accurately using a discrete device, invasive or non-invasive. Integration of such a sensor is important in the development of a closed-loop system and the technology must be rapid, selective and acceptable for continuous use by individuals. The present review provides an update on existing continuous glucose-sensing technologies, and an overview of emergent techniques, including their accuracy and limitations.

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Introduction

In 2010, the James Lind Alliance Type 1 diabetes Priority Setting Partnership was established to identify the top research priorities in diabetes, in partnership with clinicians, people with diabetes and carers [1]. One of 10 key research priorities for Type 1 diabetes was to investigate whether it is possible to monitor blood sugar levels constantly and accurately with a discrete device (non-invasive or invasive). The present paper provides an overview of current glucose-sensing techniques and their accuracy, as well as the progress made and technical challenges faced since the James Lind Alliance priorities were set.

In the UK, the National Institute of Health and Care Excellence (NICE) recommends self-monitoring of capillary blood glucose up to seven to 10 times daily, which can be painful and burdensome [2]. The commercial market for blood glucose meters is substantial, accounting for 85% of the total biosensor market [3]. In 2015, the global market for glucose sensors was estimated at US$ 15.3 bn, and is anticipated to reach US$ 31.0 bn by 2022 [4].

Type 1 diabetes research is aimed at finding effective treatments, including mimicking the intact pancreas using technologies. By increasing the frequency of the measure-and-deliver process, the ultimate goal is to establish an artificial pancreas which can maintain normoglycaemia with automated insulin delivery.

Most current commercially available continuous glucose monitoring (CGM) devices use subcutaneous needle-type sensors, and enable meaningful improvements in HbA_{1c} [5], whilst reducing exposure to hypoglycaemia [6]. The use of CGM sensors is associated with improvements in quality of life [7] and reduction in fear of hypoglycaemia [8], and is cost-effective [5]. Despite established benefits, however, factors including accuracy, reliability, usability, duration of sensor life, and calibration requirements influence the implementation of CGM in healthcare systems. Current CGM devices are susceptible to 5–15 min lag behind blood owing to diffusion of glucose to interstitial fluid [9].

The perfect CGM device would be discrete, non-invasive, accurate, intuitive and able to connect to a variety of devices to enable view, review and decision support, including automated insulin delivery. It would be acceptable and usable by people living with Type 1 diabetes, their carers, friends and families, and accessible to all. In addition, the perfect device would be intuitive for healthcare professionals, with a low burden of specialist education required to support its use. Finally, while the cost-effectiveness of CGM has been demonstrated for some groups [10], it would be sufficiently low priced to provide a cost-effective intervention for

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What's new?

- One of 10 key research priorities identified by the James Lind Alliance Type 1 diabetes Priority Setting Partnership was to investigate whether it is possible to monitor blood sugar levels constantly and accurately with a discrete device (non-invasive or invasive).
- This paper provides an overview of the latest glucose-sensing techniques, currently marketed products and their accuracy.
- To date, no device based on a non-invasive technique has successfully reached the commercial market. We review the technological challenges faced, clinical impact and future directions in continuous glucose monitoring.

everyone with Type 1 diabetes. This device does not yet exist, but multiple technical methods have been explored to work towards it, each with its own potential advantages and disadvantages.

The last decade has seen significant advances in subcutaneous needle-type sensors, but no commercial device based on a non-invasive approach has been established. In the present review, in addition to the current advances in subcutaneous glucose monitors, we discuss the developments in glucose detection in alternative sites to the subcutaneous space, and the reported accuracy of such new technologies.

Assessing accuracy and precision of glucose monitoring sensors

Multiple metrics describe glucose sensor accuracy (how close the sensor glucose measurement is to blood glucose) and precision (degree of reproducibility; Table 1). The two most frequently reported metrics are mean absolute relative difference (MARD) and Clarke error grid analysis.

A lower MARD is seen as representing better sensor performance, with a MARD of <10% representing sufficient accuracy for CGM device readings to make insulin dosing decisions [11]. Whilst this threshold is widely used, it is important to note that this value stems from *in silico* simulation, rather than an objectively characterized threshold for acceptable hypoglycaemia risk [12]. MARD is limited by the fact that it does not provide information on the direction of the error and may vary through the glucose range. In addition, there is a no standardization for the calculation of MARD, and its value might be affected by study design, with different reference standards used in different studies.

The Clarke error grid assesses CGM performance on the *y*-axis against reference glucose on the *x*-axis, assigning a clinical risk to any glucose sensor error. Results fall into one of five risk zones, labelled: A, clinically accurate; B, benign; C, overcorrect; D, failure to detect; and E, erroneous. Zones A and B are clinically acceptable. Results falling into zone C may prompt overcorrection, zone D represents a failure to detect hypo- or hyperglycaemia, and zone E represents unacceptable erroneous results.

Table 1 Definitions of accuracy measures**Accuracy measure**

	Definition	Advantages/ disadvantages
Mean difference (MD)	Mean of the sensor values – reference values	Measures size and direction of the difference compared with the reference (absolute)
Mean relative difference (MRD)	Mean difference / reference value × 100 (expressed as a percentage %)	
Mean absolute difference (MAD)	Mean of the absolute difference between sensor and reference value	Measure size but not direction (higher/lower) of the differences compared with the reference (absolute)
Mean absolute relative difference (MARD)	Mean absolute difference / reference value × 100 (expressed as a percentage %)	

Invasive and minimally invasive glucose sensors

The terms 'invasive', 'minimally invasive', and 'non-invasive' are commonly used to refer to device types employed in CGM; the first and last being clear. 'Minimally invasive' is defined to include penetration of the outer layer of the body (i.e. skin or internal epithelial tissues, such as the nasal mucosa) by <1 mm, and without requiring trained medical personnel for its application [13]. Key subtypes of invasive and minimally invasive CGM include: subcutaneous amperometric electrodes; microdialysis; intravenous implantable devices; intraperitoneal device; and microneedles.

Subcutaneous amperometric needle-type sensors

Subcutaneous needle-type sensors employ a sensor inserted beneath the skin to detect glucose concentrations within the interstitial fluid. Most currently used systems for CGM are enzyme-based.

There are three generations of enzyme-based glucose sensor (Fig. 1). The first-generation sensors estimate glucose concentration based on hydrogen peroxide production by glucose oxidase (EC 1.1.3.4), which is directly proportional to the concentration of glucose. Limitations of this include the requirement of a high operating potential (0.6 V) for measurement of hydrogen peroxide and provisions of oxygen, as well as potential deactivation of the enzyme as a result of hydrogen peroxide production.

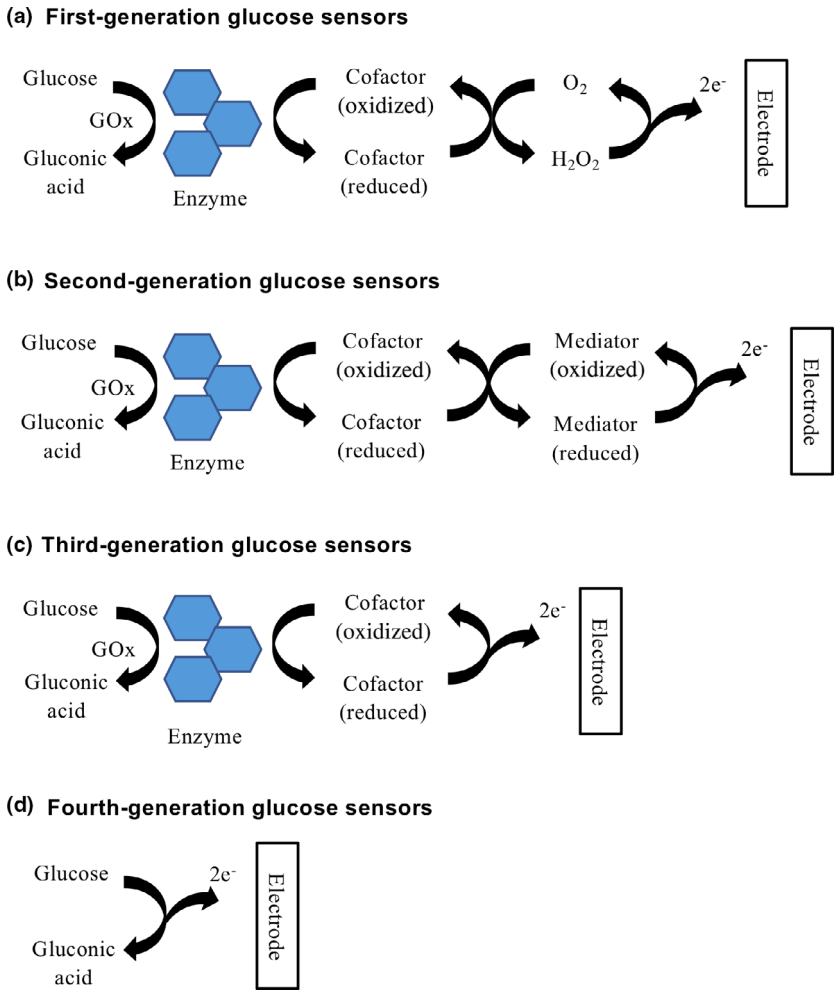

FIGURE 1 Schematic representation of electrochemical glucose detection. (a) First-generation glucose sensors based on hydrogen peroxide production by glucose oxidase (GOx), using oxygen as a cofactor. (b) Second-generation glucose sensors based on redox mediators. (c) Third-generation glucose sensors based on direct electron transfer, without artificial mediators. (d) Fourth-generation glucose sensors involving direct electro-oxidation of glucose to gluconic acid using non-enzymatic electron transfer (eg. carbon nanotubes and alloy nanostructures containing platinum, lead, gold, palladium, and rhodium).

Second-generation sensors employ a non-physiological electron acceptor to transfer electrons, resolving potential issues from oxygen availability. Most current CGM methods are based on first-generation sensor technology, except the Abbott Freestyle Libre sensor, which uses osmium as a mediator. In this case, the electrons are accepted by the osmium complex mediator and are transferred to the metal surface at lower potentials, reducing interference from other electroactive species such as acetaminophen and uric acid.

Third-generation sensors are based on direct electron transfer, not requiring mediators, while non-enzymatic electron transfer is being pursued as a fourth generation of glucose detection. These include carbon nanotube nano-electrode ensembles for selective glucose detection.

Available CGM technologies that can be used by people with Type 1 diabetes for self-management are summarized in Table 2 [14–20]. Most CGM devices display an estimate of blood glucose, with alerts and alarms for hypo- and hyperglycaemia and real-time trends in glucose changes. Flash glucose monitoring by Abbott Freestyle Libre (intermittent glucose monitoring) does not provide real-time data with alerts and alarms, but allows users to review the preceding 8 h of continuous glucose data retrospectively, along with a contemporary estimated blood glucose value and trend line. The glucose data are made available when the user chooses to swipe the reader over the sensor. At the time of writing, Abbott had obtained a CE Mark for FreeStyle Libre 2, a hybrid CGM device with optional low and high glucose alarms.

Despite the advances in technology, however, there are many barriers to device uptake, including person-related, environmental and healthcare system-related factors. Data from a re-survey of the Type 1 Diabetes Exchange Registry in 2016–2017, with 1503 adult participants, indicate that

Table 2 Comparison of current subcutaneous continuous glucose monitoring devices on market

	System						
	Guardian Connect (Sensor 3)	Enlite Sensor	Dexcom G5	Dexcom G6	Eversense	Freestyle Libre	Medtrum S7 EasySense
Sensor life	7 days	6 days	7 days	10 days	90 days/180 days (Eversense XL)	14 days	14 days
Sensor method	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Implantable (within the subcutaneous tissue)	Subcutaneous	Subcutaneous
Transmitter life	12 months	12 months	3 months	3 months	12 months (rechargeable)	3 years (reader life-span)	3 months
Calibration	Yes, every 12 h	Yes, every 12 h	Yes, every 12 h	No, factory-calibrated (user may self-calibrate if required)	Yes, every 12 h	No, factory-calibrated	Yes, every 12 h
Frequency of readings	5 min	5 min	5 min	5 min	5 min	Whenever sensor is scanned. Glucose data stored every 15 min	2 min
CE mark	2018	2011	2015	2018	2017	2014	2014
FDA approval date	2018	2013	2016	2018	2017	2008	Awaiting
Company	Medtronic	Medtronic	Dexcom	Dexcom	Senseonics	Abbott	Medtrum
Sensing technology	Enzyme electrode	Enzyme electrode	Enzyme electrode	Enzyme electrode	Optical Fluorescence	Enzyme electrode	Enzyme electrode
MARD	10.6% in abdomen; 9.1% in arm [14]	13.6% [15]	9.0% [16]	9.0% calibrated once daily [17]; 10.0% without calibration [18]	8.8% [19]	11.4% [15]	9.1% [20]

FDA, US Food and Drug Administration; MARD, mean absolute relative difference.

Table 3 Intravascular glucose monitoring systems and reported accuracy

System, company	Detection technology	Sampling site	Frequency of glucose sampling	MARD, %
Approved systems (CE-marked/FDA-approved)				
GlucoScout, Via Medical (No CE mark/FDA approved 2010)	Enzyme electrode	Peripheral venous	5 min for 72 h	5.1 [29]
OptiScanner 5000, OptiScan Biochemical (CE-marked 2017/FDA approved 2017)	Optical mid-infrared	CVC, peripheral venous	15 min	7.6 [30]
GlySure, GlySure (CE-marked 2015/no FDA approval)	Optical fluorescence	CVC	15 s	7.95 [31]
GlucoClear, Edwards LifeSciences (CE-marked 2013/no FDA approval)	Enzyme electrode	Peripheral venous	5 min	5.5 [25]
Eirus, Maquet Getinge Group (CE-marked 2009/no FDA approval)	Microdialysis, enzyme electrode	CVC	15 min	6.5 [26]
Other systems				
Glucoset (originally Invivosense)	Optomechanical	Peripheral venous	–	In development
Autosampler, Cascade Metrix	Enzyme electrode	Peripheral venous	–	In development
Automated blood glucose monitor, Luminous Medical	Near-infrared spectroscopy; then enzyme electrode	Peripheral venous, arterial	–	Unsuccessful
OPTImus, IntelliDX	Enzyme electrode	Peripheral venous	–	Unsuccessful
GluCath, Glumetrics	Optical fluorescence	Peripheral venous, arterial	5 min	13.0 [28] Unsuccessful

CVC, central venous catheter; FDA, US Food and Drug Administration; MARD, mean absolute relative difference.

CGM uptake in the USA was only 37% [21], although this had increased from 9% in 2013–2014 [22]. Cost was noted to be the most common reason for CGM discontinuation [21]. In the UK, CGM funding is only available in some areas to individuals meeting the NICE criteria, with remaining users self-funding. The criteria include: >1 episode of severe hypoglycaemia/year; complete loss of awareness of hypoglycaemia; hypoglycaemia that is causing problems with daily activities; extreme fear of hypoglycaemia; and $HbA_{1c} \geq$ 75mmol/mol (≥ 9.0%) despite testing ≥ 10 times/day [2]. Variations in funding through local payer organizations results in CGM use being varied and limited [23].

Even within a reimbursed healthcare system, however, other barriers to CGM limit uptake, including alarm fatigue, concerns about accuracy, and physical discomfort. Age is also an important factor for device uptake and use, with younger people (18–25 years) having the lowest uptake of CGM, but also having higher levels of diabetes distress and HbA_{1c} values compared with older people [21]. Younger people are more likely to dislike wearing diabetes devices, to be nervous about relying on technology, to worry about others' perceptions and to receive unwanted attention [21].

Intravenous implantable devices

Glucose monitoring technology implanted in the intravenous space can provide fast information about blood glucose; however, indwelling intravenous devices are unsuitable for permanent use in healthy adults. For critically ill people, vascular catheter CGM has the potential to become a standard of care for management, either via a radial artery, peripheral vein or central venous catheter [24]. A wide variety of detection techniques has been trialled within an intravenous device, including amperometry, near-infrared and middle-infrared spectroscopy, fluorescence spectroscopy, and optomechanical interferometry.

Intravascular devices have lower MARD values (5.1–14.2%) overall compared to interstitial fluid sensing [25]. To assess clinical performance, 26 adults undergoing cardiac surgery with cardiopulmonary bypass underwent glucose monitoring for ~23 h using both the Eirus intravascular microdialysis CGM system and the FreeStyle Libre device. Reference blood glucose values were obtained by analysing arterial blood in a blood gas test. The FreeStyle Libre was less accurate than the Eirus intravascular system (MARD 30.5% vs 6.5% [26]). Similar accuracies were reported in another study comparing the intravascular GluCath with the FreeStyle Navigator [27].

Despite improved accuracy, widespread use of intravenous glucose monitoring devices has been limited (Table 3 [25,26,28–31]). Thrombus formation can occur and result in pulmonary emboli from central venous catheter lines or peripheral ischaemia from clots in arterial lines. One study reported thrombus formation in 21% of arterial devices and up to 66% in venous devices. Localized inflammatory reactions have been reported, with diabetes exacerbating such effects [28]. Heparin may mitigate some of the risks of thrombi, but may result in erroneous coagulation tests and may increase the incidence of heparin-induced thrombocytopenia [28].

Microneedles

Microneedle techniques have been explored for interstitial fluid sensing and have been extensively used for therapeutic

drug and vaccine delivery applications [32]. This approach can offer a minimally invasive method for glucose sensing via a microneedle patch platform which perforates the stratum corneum without penetrating the full thickness of the skin.

Many microneedle designs have been published, with a variety of fabrication methods and materials employed [33]. Hollow microneedles, in contrast to solid microneedles, have been associated with blockage as a result of protein deposition, requiring offline analysis of the fluid extracted, and are more likely to be mechanically fragile [13].

The first human data from solid microneedle CGM for durations of up to 24 h have been reported [34]. Results reported user acceptability, with no adverse events and MARD accuracy of 9%, with >94% of the data points in the A and B zones of the Clarke error grid [34].

The K'Watch Glucose (PKVitality, Paris, France) uses 0.5-mm microneedles under a wearable watch to probe interstitial fluid. The product has received a H2020 European Union grant for phase I trials.

Non-invasive glucose monitoring techniques

Multiple methodologies have been pursued to develop a non-invasive continuous glucose sensor. These include transdermal, optical and thermal techniques.

Transdermal techniques

Reverse iontophoresis

The GlucoWatch® was the first transdermal non-invasive glucose sensor approved by the FDA in 2001. Worn as a wrist-watch, the system uses reverse iontophoresis to measure glucose. This involves applying a low-level electrical current between two electrodes across the skin to extract fluid for secondary glucose sampling by a glucose oxidase-based platinum electrode (Fig. 2). The skin is able to filter off large molecules, reducing biofouling and electrochemically active fouling. Limitations of this technique include an extended warm-up period, time lag, calibration requirement, skin irritation, and sweat preventing accurate operation.

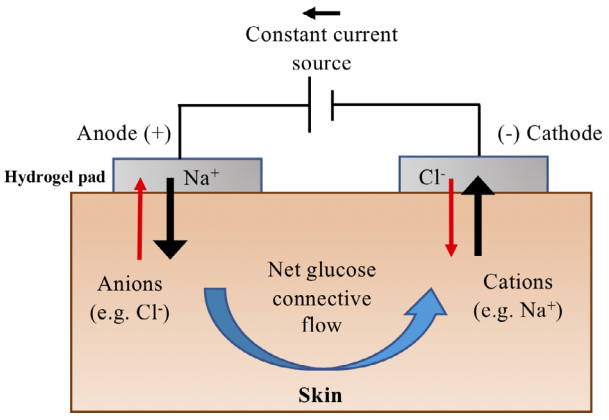

FIGURE 2 Principle of glucose extraction by reverse iontophoresis.

In addition to these limitations, the GlucoWatch was found not to be useful in detecting nocturnal hypoglycaemia over 24 h in clinic studies, with reported sensitivity of 23% for glucose concentrations <3.3 mmol/l and a 51% false-alarm rate [35]. Consequently, the device was withdrawn from the market in 2008.

To address these drawbacks, a wearable tattoo-based non-invasive glucose monitoring platform has been proposed, combining reverse iontophoretic extraction of interstitial glucose and an enzyme-based amperometric biosensor [36]. This proof of concept obviated the discomfort of the Glucowatch by reducing the applied iontophoretic current for interstitial fluid extraction [37].

The tattoo-based device still requires invasive calibration with blood glucose levels; however, a proposed method to develop a completely non-invasive glucose monitoring system could utilize simultaneous sodium extraction to allow calibrated glucose measurements [37,38]. The proposed method uses diffusion and osmotic flow to extract sodium ions [38]. The interstitial sodium concentration is stable and comparable between individuals on a daily basis; thus, the ratio of glucose to sodium is proportionate to glucose through a determinable correlation constant [37].

Another technology using reverse iontophoresis, is SugarBeat (Nemaura Medical, Loughborough, UK). It is a patch-type sensor, due for launch in early 2019. No peer-reviewed publications have been noted at the time of writing.

Impedance spectroscopy

Impedance spectroscopy is another transdermal technique using a small alternating current, and the impedance of the tissue to the current flow is recorded as a function of frequency. Glucose is indirectly measured by its concentration-dependent interaction with red blood cells, resulting in a modified membrane potential [39]. In 2003, the company Pendragon developed a wrist glucose monitor, the Pendra; however, a post-marketing validation study revealed poor accuracy, with a MARD of 52% and 4.3% of the Pendra readings in the potentially dangerous zone E of the Clarke error grid [40]. The device was withdrawn from the market.

Sonophoresis

Sonophoresis uses low-frequency ultrasonography (<100 kHz) to increase cutaneous permeability to interstitial fluid, enabling a non-invasive method for glucose monitoring. Whilst this method enables glucose detection, it has only been tested in rats, where results have indicated some degree of skin irritation and high error ranges (mean relative error 23%) [41]. Prototyping has not yet reached the stage of human subject testing.

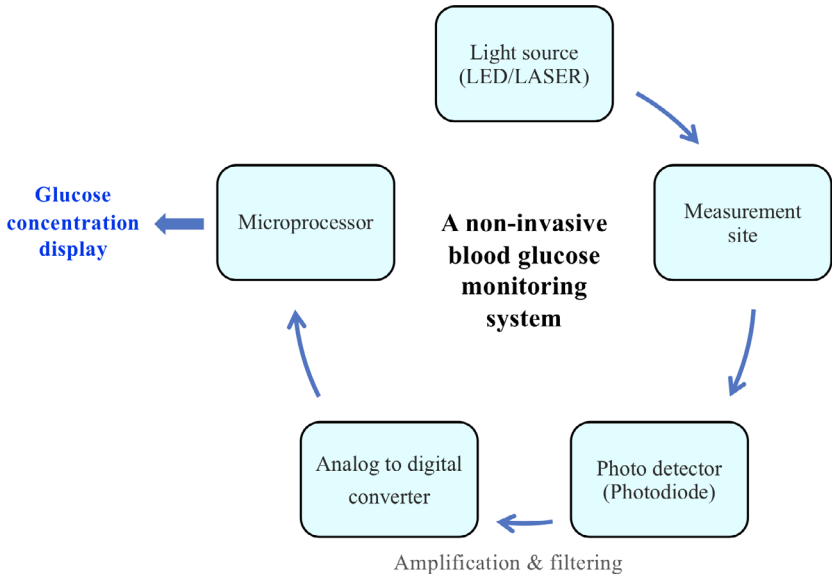

FIGURE 3 Requirements of a non-invasive optical blood glucose monitoring system.

Skin suction blister technique

The skin suction blister technique uses a vacuum to form small interstitial fluid-filled blisters, a few millimetres in diameter at the epidermal–dermal junction, from which glucose can be measured. The technique has been reported to be painless and well tolerated, with minimal risk of infection [42]; however, the suction procedure may result in cell damage, leading to increased concentration of lysosomal and cytoplasmic enzymes. No devices are currently using this technique.

Optical techniques

Compared to transdermal technology, optical technology offers more investigative options. Variable frequencies of light are used to detect glucose using optical transducers, taking advantage of the different ways th at light interacts with glucose molecules in a concentration-dependent manner (Fig. 3); however, despite attracting significant research interest, the medical market lacks a product for non-invasive optical CGM. The Senseonics Eversense (Senseonics Holdings, Inc., Germantown, MD, USA) CGM device is an implantable glucose sensor, lasting up to 6 months, but has the drawback of being invasive in nature.

The challenges for effective CGM using light techniques are multiple. The detection of a non-invasive signal, generated by low level of glucose is difficult to measure because of dynamic and complex background signals (i.e. water, haemoglobin and lipids which overlap the weak spectra of glucose). Physical variables, such as thickness of tissue, scattering properties and temperature of the tissue at the measurement site, can affect readings. Furthermore, the instrumentation device requires several components: a light-emitting diode, a photodiode, an analogue to digital convertor and an amplifier with micro-processer-based circuitry to convert the values in to a corresponding blood glucose value [43]. Integration within a non-invasive portable device for CGM remains the challenge.

Glucose detection based on optical approaches can be broadly classified as (1) fluorophore-based and (2) direct (nonfluorophore)-based techniques.

Fluorophore-based optical sensors

The fluorophore-based approach uses an affinity sensor principle by which glucose and a fluorophore bind competitively with a receptor. Concanavalin A is a carbohydrate-binding protein with four glucose-binding sites which can be used as the receptor molecule. Preferential binding of glucose to concanavalin A compared with fluorescein-labelled dextran, results in increased free fluorescein-labelled dextran and increased emission (Fig. 4a) [44].

Using a combination of various design and screening approaches, many combinations of fluorescent sensor for glucose have been studied, with varying degrees of success. Changes in fluorescence to correlate with glucose concentration can be detected either by using combinations of environment-sensitive dyes or by using Förster (or fluorescence) resonance energy transfer (FRET) pairs.

Fluorescence emission occurs from FRET pairs when they are within atomic distances (Forster radius) of each other [45]. In the presence of glucose, which changes the conformation, the distance between the two fluorophores is increased, quenching FRET-induced fluorescence emission (Fig. 4b). Glucose concentration can thus be evaluated [44]. Although this technique is promising, no non-invasive device based on this concept has been approved for clinical use, as yet.

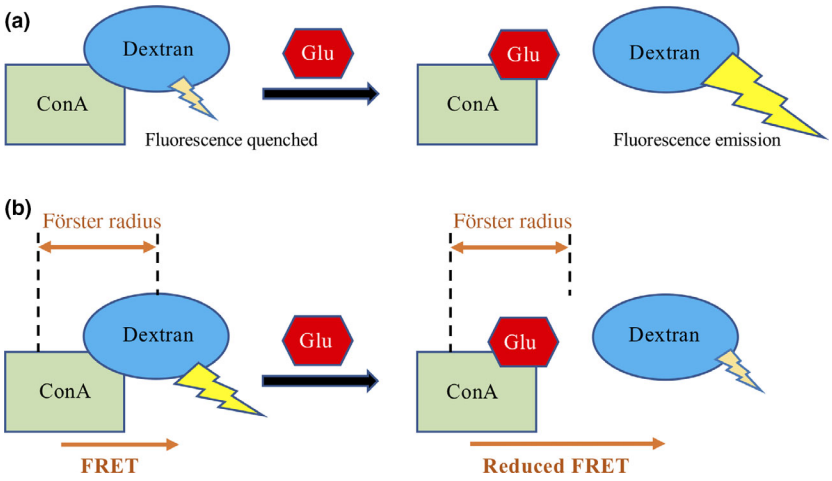

FIGURE 4 Optical detection of glucose using fluorescence. (a) The binding of Concanavalin A (ConA) to fluorescein-labelled dextran results in charge transfer, and a subsequent reduction of fluorescence intensity from the fluorescein-labelled dextran. Glucose preferentially binds to ConA compared to fluorescein-labelled dextran, thereby increasing free (unbound) fluorescein-labelled dextran. As a result, in the presence of glucose, there is an increase in the intensity of the fluorescence emission. Thus, the higher the glucose concentration, the higher the fluorescence intensity of fluorescein-labelled dextran. (b) Preferential binding of glucose to ConA, increases the distance between ConA and dextran (i.e. greater than the Förster radius), hence leading to a decrease fluorescence resonance energy transfer (FRET)-induced fluorescence emission.

Whilst Eversense cannot be classified as a non-invasive CGM device (Table 2), it has successfully managed to integrate all the components required in an optical sensing system and is therefore discussed in this section. It uses a non-enzymatic glucose sensor based on a fluorophore-linked hydrogel. Glucose reversibly binds to a boronic acid indicator (which acts as a glucose receptor), disrupting electron transfer, and resulting in increased fluorescence intensity [46]. The optical system is contained within a capsule comprising light-emitting diodes, and an antenna, which communicates with the smart transmitter. An externally worn smart transmitter remotely powers and communicates with the inserted sensor, with information communicated wirelessly via Bluetooth to a smartphone-based app [46].

Direct (non-fluorophore-based) optical sensors

Non-fluorophore-based optical detection of glucose utilizes light of variable frequencies to investigate changes in the absorbance, reflection or refraction (scattering) of tissue containing various concentrations of glucose.

Absorption spectroscopy. Absorption spectroscopy is a widely employed other analytes. The presence or concentration of a substance is determined by measuring how it interacts with light. A wide variety of optical spectroscopic methods have been developed, based on different excitation and detection principles, operational range, as well as scope of application. These include, ultraviolet (<400nm), visible (~400–700 nm), near-infrared (~600–2500 nm) and middle-infrared wavelengths [47]. All spectroscopic methods face multiple problems, including scattering of light.

Raman spectroscopy. Raman spectroscopy assesses scattering of light from a single wavelength. Water has weak scattering indices, and therefore Raman is subject to less interference from water compared to middle-infrared or near-infrared spectroscopy. However, this type of spectroscopy has overall weaker signals compared with other technologies, requiring powerful detectors for physiological concentrations of glucose. The Raman signal is also susceptible to turbidity, haematocrit, skin thickness and melanin.

The C8 MediSensors Optical Glucose Monitoring System relied on Raman spectroscopy providing continuous glucose measurement every 5 min. One of its main advantages was the lack of requirement for calibration. The percentage of points in zone A and in the A+B CEG zones were 53% and 92%, respectively [48]. It received a CE Mark in 2012. In 2013, C8 MediSensors filed for bankruptcy following technical challenges [49].

Polarimetry. Polarized light refers to light whose electric field oscillates in a specific manner, e.g. a planar, elliptical or circular manner. The concentration of glucose can be determined when polarized light is passed through a solution of an optically active substance, and the rotation of its polarized plane is measured using a polarimeter.

In vivo animal trials across 3 separate days, using dual-wavelength polarimetry, have shown clinically acceptable glucose detection, with an overall MARD of 4.5% and 100% of measurements falling within zone A on a Clarke error grid [50]. Further human studies are required.

Optical coherence tomography. Optical coherence tomography (OCT) uses near-infrared light, backscattered from tissues, which is combined with light returned from the reference arm of an interferometer and the resulting signal is detected by a photodetector. A two-dimensional image of optical scattering is formed from internal tissue

microstructures in a way that is analogous to ultrasound imaging. In a feasibility study in 33 participants using an OCT-based device (Sentris-100TM, GlucoLight, Bethlehem, PA, USA), based on 236 matched points, Clarke error grid analysis indicated 83% of measurement were in zone A and 16% in zone B [51]. GlucoLight no longer exists.

Occlusion spectroscopy. Occlusion spectroscopy measures the scattering angle when light interacts with glucose molecules, similar to OCT; however, this technique exploits arterial blood flow through temporary cessation of blood flow by 'occlusion', which enhances the red near-infrared signal.

Using this methodology, OrSense NBM 200G gained CE approval in Europe in 2007. The system consisted of a finger-attached sensor probe operating with red/near-infrared light. Additionally, it contained pneumatic cuffs that produced an oversystolic pressure around the finger to occlude blood flow, generating a dynamic optical signal for glucose monitoring. Clinical trials conducted in 23 individuals with a total of 1671 paired glucose values showed 95.5% of device readings were in the Clarke error grid A and B zones, with a MARD of 17.2% [52]. Although this product received CE approval, it has never been commercialized.

Photoacoustic spectroscopy. Photoacoustic spectroscopy is a variant of optical spectroscopy that uses an acoustic (ultrasound) detector as opposed to an optical sensor. This is based on the principle that light absorption causes ultrasound waves. Tissue is illuminated by a light source at a specific wavelength and the absorbed radiation causes localized heating, leading to volumetric expansion which is then detected as an ultrasound pulse [53].

In recent years, photoacoustic spectroscopy has demonstrated higher sensitivity relative to optical absorption spectroscopy for non-invasive glucose detection [54], but is susceptible to changes in skin condition, i.e. hand washing and drying, due to interference by skin secretion products or water. In clinical studies, from 76 measurements in five independent experiments with a healthy participant and a participant with diabetes, 100% of measurements fell into zones A and B of the Clarke error grid, with a MARD of 14.4% [55]. Further larger-scale studies are required using this methodology.

Despite much promise, challenges relating to requirements of power and light source, detection, processing and implementation within a fast, reliable, discrete device, means light technology remains some time away from being implemented in the near future.

Thermal techniques

Thermal microdevices have the capability to detect small changes in heat resulting from biochemical processes. Glucose sensors may incorporate thermal properties for non-invasive monitoring, using the principle that cutaneous microcirculation is dependent on glucose concentration. Thermal infrared is used as a surrogate measurement of periodic temperature variations in the skin, assessing middle-infrared light scattering in the skin at different tissue depths.

Using a similar principle, microwave signals can also be used in conjunction with a thermistor, placed in the glucose sensor head, to monitor the fluctuations of skin temperature. Preliminary trials in 24 individuals for ~3 h each, within a clinic setting, show a MARD of 12.5% (Clarke error grid: 98% in zone A and B) [56]. Further large-scale research into thermal-based glucose monitoring is required.

Glucose monitoring in the eye

The fluid surrounding the eye and ocular tissue, is more easily accessible than blood, interstitial fluid or urine. The correlation of tear glucose and blood glucose has been reported since the 1980s [57]; however, discrepancies in correlation have been reported. This can be attributed to the different tear collection methods (filter paper or microcapillary), or could be attributable to differences in techniques used to quantify tear glucose. The use of glucose-sensing contact lenses is a much-desired paradigm, and presents the opportunity to not only correct vision, but to monitor glucose levels continuously in the tear fluid [58].

Google[X] lab (Mountain View, CA, USA) and Novartis (Basel, Switzerland) incorporated an electrochemical battery-operated enzymatic glucose sensor, utilizing the glucose oxidase, in a microchip placed between two layers of a soft contact lens. The sensor subsequently relayed glucose data to a handled mobile device. The reaction is enabled through the production of hydrogen peroxidase at the working electrode. Disadvantages of such an approach include the build-up of corrosive hydrogen peroxide as a by-product, as well as potential interference from electroactive analytes in the ocular fluid.

Other practical issues limiting the use of smart contact lenses include use of opaque and brittle components required for sensors and circuit chips which can block user's vision and potentially damage the corneal surface. Furthermore, many users may choose not to wear the contact lens overnight when hypoglycaemia detection may be most desired.

To address some of these pre-existing issues, a smart contact lens made of transparent and stretchable nanomaterials for glucose sensors, wireless power transfer circuits, and display pixels has been designed to visualize sensing signals in real time [59]. In addition to the biomechanical challenges, however, whether correlation between glucose in ocular fluid compared to blood will be sufficient for contact lenses to be part of a closed-loop system remains questionable. Research on the glucose-sensing lens has now ceased because of insufficient consistency in the correlation between lacrimal fluid and blood glucose concentrations [60].

Glucose monitoring in the respiratory tract

Breath analysis is another site of potential glucose sensing, assessing volatile organic compounds, generated as by-products from metabolic pathways [61]. Volatile organic compounds can be analysed continuously using a so-called electronic nose (eNose). Biomarkers for diabetes include ethanol, acetone and methyl nitrite [62]. Acetone levels in individuals with Type 1 and Type 2 diabetes have been reported with diagnostic accuracy of 74%.

The eNose has garnered significant interest for clinical use, but the device requires a controlled external atmosphere, with many other factors affecting acetone levels, such as fasting, diet and exercise, thereby limiting its use. In a study of critically ill intubated adults, continuous exhaled breath analysis using eNose was unable to predict blood glucose levels accurately [63].

Integration of technologies and sensors

As a result of the complexity of human body composition and physiological processes, no single non-invasive technique to date has successfully provided clinical results sufficiently accurate for glucose sensing for people with Type 1 diabetes. The future for non-invasive monitoring may be the integration of multiple sensors. Combining sensor signals with monitoring of other perturbing effects that lead to deteriorations in glucose-sensing signal quality, such as environmental (temperature and humidity variations) and physiological effects (blood perfusion and sweat events), may provide more reliable non-invasive glucose monitoring [64]. For example, bio-impedance spectroscopy has been integrated with photoelectric sensors [64], while another approach has combined impedance spectroscopy and near-infrared spectroscopy, with a MARD of 8.3% [65].

Already CE-marked in 2014 for use in individuals with Type 2 diabetes and prediabetes, Glucotrack (Integrity Applications, Ashdod, Israel) determines glucose levels using three non-invasive techniques: thermal heat conduction; ultrasonography; and impedance spectroscopy. Each method estimates glucose levels independently, and a weighted average of the three estimated values is used to calculate the final estimation value. The sensors are contained within a personal ear-clip, which limits its use as a tool for continuous monitoring; however, clinical trials in 172 adults, for 8–10 h over 2–3 non-consecutive days, indicate consistent accuracy, with a reported MARD of 18.8%, and 97.6% of glucose readings within zones A + B of the Clarke error grid. Performance did not depend on the demographic profiles of its users [66]. Although the device received CE approval, its commercialization has been limited.

Another system uses integration of multiple sensor variables such as impedance spectroscopy at low and high frequency and optical properties, temperature and humidity [67]. Results in nine volunteers over 72 h showed that 100% of the estimated glucose values fell within the clinically acceptable zones A and B in Clarke error grid analysis (92.86% were in zone A [67]).

Nanotechnology

Nanotechnology involves the development and production of devices or structures with dimensions <100 nm, or uses characteristic effects and phenomena in this size range (quantum effects). Overall, nanoscale properties have several advantages, including higher surface areas (therefore larger currents and faster responses) and improved catalytic activities. As a result, this technology is associated with a higher signal-to-noise ratio, increased selectivity and improved sensitivity of the glucose sensor measurement [68].

Well-studied nanomaterials are nanotubes, particularly carbon nanotubes, which may be single- or multi-walled. The nanotube functions as a light amplifier [69], with glucose detection occurring via similar principles to those of ordinary glucose sensors, i.e. glucose oxidase.

Despite significant advances with carbon nanotubes, the main concern is still the potential risk of toxicity, which has been shown in both *in vitro* and *in vivo* studies. Toxicity can be dependent on various factors, including the method and duration of exposure, length, stiffness and concentration. Properly surface-functionalized carbon nanotubes have not induced obvious toxicity, whereas raw carbon has induced pulmonary toxicity and mechanical blockage of the upper airways in animal models [70]. Further studies are needed to evaluate the safety of carbon nanotubes, and mediators, before their widespread use as a potential glucose sensor.

Conclusions

Many glucose-sensing technologies are under development, with the final goal of enabling self-management and improving quality of life in people with Type 1 diabetes. Since the James Lind Alliance research priorities were established, it has become feasible to continuously, and with relative accuracy, monitor blood glucose levels using minimally invasive technology. However, despite support for CGM use in Type 1 diabetes, with a growing evidence base, routine implementation in treatment pathways has not yet been fully achieved. In the UK, regional variations in funding reflect the challenging nature of adopting new technologies into a resource-limited public health system. Other barriers to CGM uptake include person-related factors, such as alarm fatigue and physical discomfort.

Multiple non-invasive approaches to glucose-sensing have been evaluated at the bench and clinically. Although initially promising, non-invasive devices have limitations of low sensitivity, specificity and accuracy. The indirect nature of non-invasive approaches subjects them to a relatively low signal-to-noise ratio and poor accuracy attributed to interference by other bodily processes. Some techniques require

specialist light, sound or heat sources, and most require complex signal processing which may limit portability. As a result, there are no non-invasive devices commercially available at present, and this may remain the case for some time, despite early promise in a controlled clinical research environment.

The immediate future of glucose-sensing technology is likely to be improved iterations of subcutaneous electrochemical sensors, perhaps in combination with a second sensing method for redundancy and confirmation. Innovations integrating CGM data with wearable physiological sensors to support fast and accurate diabetes management are being developed, ensuring that the continuous glucose data are interpreted in context for automated or supported insulin delivery. While there remain challenges to implementing existing, evidence-based technologies into routine clinical care, the key focus for clinicians should be on support and education of healthcare professionals, and of people living with Type 1 diabetes, to successfully adopt available CGM technology.

Competing interests

None declared.

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