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EDITORIAL

Glucose sensing technology—current practice?

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There are approximately 28,500 people with type 1 diabetes (T1DM) in the Republic of Ireland. Frequent self-monitoring of blood glucose (SMBG) allows accurate and directed self-management for patients with T1DM and is imperative in attaining glycaemic targets [1]. From testing for glycosuria to measuring capillary blood glucose levels with a portable glucometer, there have been considerable technological advances over the past 60 years to facilitate SMBG in patients with diabetes. However, even when patients test their glucose level 4–5 times per day, they remain at risk of hypoglycaemia and significant glucose variability. Hence, the development of continuous glucose monitoring systems (CGMS) has been a welcome addition to the ever-evolving field of diabetes technologies.

The concept of glucose sensing technology is not new. In 1962, Clark and Lyons described the principle of 'enzyme containing membrane electrodes' [2]. They proposed utilising a glucose permeable membrane to trap a thin layer of glucose oxidase containing solution and measuring the oxygen consumption by the enzyme catalysed reaction (i.e. glucose + O_2 —> gluconic acid + H_20_2) with an adjacent electrode [2]. This concept was refined further by Guilbault and Lubrano, who described an enzyme electrode for glucose detection based on the measurement of the hydrogen peroxide product of the reaction [3]. Subsequently, a third strategy for electrochemical sensing was developed. The addition of a redox mediator to the reaction, to facilitate the efficient transfer of electrons between the glucose oxidase enzyme and the electrode is the principle on which the current market leading sensors are based.

Thirty years after Clark and Lyons published their seminal work, Moatti-Sirat et al., implanted glucose sensors into the subcutaneous tissue of rats and demonstrated accurate estimations of blood glucose concentrations by the sensors for up to 10 days [4]. It is now clear that a good linear relationship exists between subcutaneous interstitial fluid (ISF) glucose concentrations and plasma glucose levels. However, there is approximately a 5–10-minute delayed response in post prandial ISF measurements compared to blood glucose concentrations [5]. In 2006, the FDA approved the DEXCOM SEVEN device, the first continuous glucose monitoring (CGM) system for patients with diabetes. Since then, several CGM systems have become commercially available and emerging research is now focussed on developing non-invasive sensing techniques, i.e. optical/transdermal sensors.

CGM provides patients with information on the duration, magnitude and frequency of blood glucose fluctuations by measuring ISF glucose levels every 1–10 minutes. Data can be accessed by the patient in "real-time" or retrospectively depending on the sensor [6]. This facilitates the identification of glucose trends and may help prevent episodes of hyper- or hypo- glycaemia. Some sensors have an additional alarm feature which alerts the patient when they are hyper- or hypoglycaemic. Multiple clinical trials have demonstrated that CGM is better than SMBG for improving glycaemic control in select patient groups. Battelino et al. compared CGM with SMBG in 120 adults and children using multiple daily injections (MDI) over a 6-month period and demonstrated improved glycaemic control and reduced time spent in hypoglycaemia in those patients using CGM [7]. Sensor technology has also been used in conjunction with insulin pump therapy with encouraging results. In the STAR3 study, sensor augmented pump (SAP) therapy was associated with significant reductions in glycated haemoglobin (HbA1c) (− 0.8%) compared with MDI (− 0.2%) in almost 500 patients after 12 months [8]. Some SAPs have a threshold suspend feature which interrupts the delivery of insulin at a preset sensor glucose value. These are particularly useful for patients with impaired awareness of hypoglycaemia and have been shown to significantly reduce the frequency of nocturnal hypoglycaemia compared with SAP alone [9].

Despite the promising results emerging from clinical trials, there are a number of limitations to CGM. Firstly, patient selection is of critical importance. The American Diabetes

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Association recommend the use of CGM in selected patients with T1DM who require intensive insulin regimes and support its use as a supplement to SMBG in patients with problematic hypoglycaemia or impaired awareness of hypoglycaemia [10]. Poor compliance with CGM devices has been reported in patient groups below 24 years old, and non-adherence to CGM mitigates its potential metabolic benefits [11]. Secondly, patients using CGM require extensive diabetes education to facilitate appropriate interpretation of the data to derive maximum benefit from the device. Furthermore, patients must be relatively technically adept. A third limitation of sensors is the need for regular calibration with blood glucose values, up to four times per day to ensure the accuracy of interstitial glucose measurements. As mentioned previously, there is a physiological delay between ISF glucose measurements and blood glucose measurements of approximately 5 minutes. However, in practice, lag times are variable and are dependent upon a number of factors including CGM filtering regimes, sensor size and depth of sensor in the tissue [12].

Though glucose sensing technology remains imperfect, there have been significant technical improvements over the past 15 years. Abbots' FreeStyle Libre flash glucose monitoring system has become available in Ireland from 2016 and has garnered a lot of interest from both the media and patients with diabetes alike. The FreeStyle Libre system is composed of a discreet sensor and a reader, which displays the glucose data collected by the sensor when placed in close proximity to the sensor. The system is factory calibrated and therefore does not require calibration with blood glucose measurements. Despite this, the FreeStyle Libre system remains accurate at predicting capillary glucose values with a mean absolute relative difference (MARD) of 11% compared to SMBG [13]. Interestingly, the reported MARD for the DEXCOM sensor is 12.5% [14]. Though not reimbursed by the HSE at the moment, the FreeStyle Libre system is available to buy through Abbots website and does not require a prescription. Our clinical experience suggests high levels of patient satisfaction with the FreeStyle Libre system, with many finding the data on glucose trends particularly advantageous in their diabetes self-management. In 2016, the IMPACT trial comparing flash glucose monitoring to SMBG in patients with well-controlled T1DM was published. In this study, Bolinder et al. demonstrated a 38% reduction in hypoglycaemia with the FreeStyle Libre system compared to SMBG [15]. As patients in the intervention group scanned their sensors three times more frequently than the control group performed SMBG, it suggests that increased knowledge of glucose values and trends allowed patients using the FreeStyle Libre system to intervene earlier to prevent hypoglycaemia [15]. Cost-benefit analyses based on the results from the IMPACT trial, confirm the cost effectiveness of the flash monitoring system in patients with well-controlled T1DM on intensive insulin regimes compared with SMBG, but further studies are required to assess the utility of this system in other cohorts [16]. At the moment in Ireland, it is not clear if, when and for whom reimbursement for this system will be possible.

There is no doubt that CGM offers advantages over intermittent glucose monitoring for certain patients. Though significant progress has been made, there is a need for further improvements in glucose sensing technology to facilitate accurate, real-time glucose measurements in a cost-effective, non-invasive way.

Compliance with ethical standards

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

Human and animal rights and informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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