

## In Pursuit of an Ideal – A Perspective on Non-Invasive Continuous Glucose Monitoring

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### Abstract

Diabetes is one of the most common non-communicable diseases globally, and is the fourth or fifth leading cause of death in many countries. Medical technology for the management of diabetes has advanced steadily since the discovery of insulin in the early 20th century. Today, individuals with diabetes benefit from home-use blood glucose meters, continuous insulin pumps and, most recently, continuous glucose monitoring (CGM). Numerous studies have shown that frequent use of real-time CGM can improve glycaemic control with reduced risk of hypoglycaemia. However, current CGM devices have not been wholeheartedly embraced, limiting their potential. A CGM device that is accurate, non-invasive, pain-free and non-intrusive to daily activities could drive increased adoption and use of CGM, potentially improving health and quality of life for many individuals living with diabetes.

### Keywords

Diabetes, continuous glucose monitoring, non-invasive continuous glucose monitoring, real-time continuous glucose monitoring, HbA<sub>1c</sub>, tight glycaemic control, ideal glucose monitor

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Approximately 366 million individuals worldwide have type 1 or type 2 diabetes, and it is likely that global prevalence will rise to 552 million individuals by 2030.<sup>1</sup> Currently, an estimated 4.6 million deaths are attributed to diabetes annually.<sup>1</sup> Undisputedly, the best way to address this 'diabetes epidemic' is through a global commitment to prevention, early diagnosis, accurate monitoring and effective treatment.

### Criticality of Tight Glycaemic Control

The comprehensive, 10-year Diabetes Control and Complications Trial (DCCT) in 1993, which established glycated haemoglobin (HbA<sub>1c</sub>) as a gold standard measure of long-term glycaemic control, clearly demonstrated that individuals with type 1 diabetes who kept blood glucose levels as close to normal as possible for as long as possible had less chance of developing disease-related complications.<sup>2–4</sup> Since that time, other studies have confirmed the importance of tight glycaemic control with minimal glucose excursions in reducing disease-related complications not only in type 1 diabetes, but also in type 2 diabetes.<sup>5–9</sup> Today, individuals with diabetes are encouraged to maintain blood glucose at normal or near-normal levels. Furthermore, those who take insulin injections are encouraged to follow intensive treatment programmes with tight glycaemic control targets, which require frequent glucose monitoring.<sup>10</sup>

### Barriers to Tight Glycaemic Control

Despite advances in technologies and therapeutics, intensive treatment of type 1 diabetes frequently fails to achieve target HbA<sub>1c</sub> as recommended by the DCCT more than 15 years ago.<sup>11</sup> Many individuals – including those who measure blood glucose several times daily – still experience postprandial hyperglycaemia and asymptomatic nocturnal

hypoglycaemia.<sup>12,13</sup> These findings suggest that tight glycaemic control is difficult to achieve for many individuals with diabetes. There are a variety of reasons for this, including fear of hypoglycaemia, poor adherence to self-monitoring of blood glucose (SMBG) and lack of continuous data about glucose dynamics.

### Hypoglycaemia

Hypoglycaemia can lead to neurologic, cognitive and cardiovascular dysfunctions, and if left untreated, death.<sup>13</sup> Frequent hypoglycaemic episodes can cause 'hypoglycaemia unawareness', a condition that leaves an individual unable to recognise hypoglycaemia when it occurs. As the most feared complication of insulin therapy,<sup>14,15</sup> hypoglycaemia is the main reason why individuals with diabetes who take insulin injections are hesitant to pursue intensive blood glucose control.<sup>11</sup>

### Insufficient Monitoring

Despite ever-increasing evidence that tight glycaemic control reduces risk of disease-related complications, many individuals with diabetes do not monitor glucose often enough to achieve this objective.<sup>16–19</sup> One study showed that only 40 % of those with type 1 diabetes and 26 % of those with type 2 diabetes performed SMBG at least once a day,<sup>20</sup> and several other studies have demonstrated low SMBG adherence.<sup>21–23</sup> The reasons are numerous, but often include cost, pain, inconvenience and complexity of testing requirements.<sup>18,21,24–26</sup>

### Incomplete Data

The rate of formation of HbA<sub>1c</sub> is directly proportional to the ambient glucose concentration. Since erythrocytes are freely permeable

to glucose, the level of HbA<sub>1c</sub> in a blood sample provides a glycaemic history of the previous 120 days, the average lifespan of an erythrocyte. The test, however, provides no information about glycaemic excursions. So, an individual could have numerous excursions that, in essence, cancel each other out to deliver an acceptable HbA<sub>1c</sub> value. Such a situation would put that individual at risk of developing diabetes-related complication.<sup>2-5,11</sup> Even SMBG provides only a spot measurement of an individual's glucose level, with no information about rate or direction of change. Unless performed every 15–30 minutes, which is impractical given requirements for finger-stick blood samples and cost of test strips, SMBG simply cannot provide enough information about direction, magnitude, duration, frequency and cause of glucose fluctuations to provide a complete picture of glucose dynamics over time. Without complete information about time spent hyper-, hypo- and euglycaemic, it is difficult for an individual to achieve tight glycaemic control.

### Overcoming Barriers – Continuous Glucose Monitoring Improved Glycaemic Control

Real-time CGM (RT-CGM) became available around 2006. It provides a complete picture of glucose levels over time and in the context of daily activities. Since then, a large number of studies have shown that RT-CGM can improve glycaemic control with reduced risk of hypoglycaemia.<sup>27-39</sup> A recent review of 19 randomised controlled trials (RCTs) concluded that RT-CGM lowered HbA<sub>1c</sub> in adults with type 1 diabetes.<sup>40</sup> In addition, of nine RCTs focused on the use of RT-CGM data verified by SMBG data to make dynamic therapeutic adjustments for people with diabetes,<sup>32,41-45</sup> seven demonstrated benefit. Four showed improved glycaemic excursions, reduced glycaemic variability, decreased time spent in hypo- and hyperglycaemia, and improved HbA<sub>1c</sub> with RT-CGM;<sup>41,43-45</sup> one reached similar conclusions but did not evaluate HbA<sub>1c</sub>;<sup>32</sup> and two showed improved HbA<sub>1c</sub> with frequent use of RT-CGM.<sup>27,46</sup> Although the three remaining studies did not find a significant benefit of RT-CGM on metabolic control, one noted decreased use of CGM due to skin irritation<sup>42</sup> and the other two involved less than daily use of CGM,<sup>47,48</sup> which could have affected results. Finally, several studies have observed that RT-CGM can improve glycaemic control when used as part of an insulin pump regimen if used at least 70 % of the time.<sup>8,49,50</sup>

Furthermore, the benefit of RT-CGM extends to type 2 diabetes. A recent review of published studies concluded that RT-CGM can improve glycaemic control in individuals with type 2 diabetes.<sup>51</sup> And, two RCTs of CGM in type 2 diabetes drew similar conclusions,<sup>52,53</sup> suggesting that RT-CGM might benefit a wider range of individuals with diabetes than previously thought. Other studies have shown CGM to be useful for modifying diet and exercise to improve glycaemic control<sup>51,54</sup> and reduce risk factors for diabetes-related complications.<sup>51,55,56</sup> Real-time CGM has also been used to detect postprandial hyperglycaemia<sup>12,57</sup> and determine postprandial glycaemic profiles following ingestion of meals of different composition.<sup>58</sup> This is of particular benefit given the prominent role that postprandial hyperglycaemia can play in the development of vascular complications of diabetes.<sup>59</sup>

### Limited Adoption and Use

Despite the benefit of RT-CGM, it has not been wholeheartedly embraced for reasons such as complexity, inappropriate

expectations, invasiveness, cost, pain, discomfort, risk of infection and the degree to which it is perceived to interfere with daily life.<sup>60</sup> These issues have limited willingness to begin CGM as well as frequency of CGM use once started. Since clinical studies have shown a linear relationship between increased use of CGM and lowered HbA<sub>1c</sub>,<sup>29,61</sup> lack of adoption and infrequent use are serious concerns. All current CGM devices are invasive, requiring insertion of a needle catheter into the subcutaneous adipose tissue to measure glucose in the interstitial fluid. The insertion injures the local microvasculature, extracellular matrix of structural proteins and adipose cells, and the wound fills with red blood cells, platelets, coagulation proteins and cellular debris which can compromise sensor performance.<sup>62-64</sup> Both the warm-up period required for sensor stability and sensor performance depend to a large degree on the extent of tissue injury, with more extensive injury requiring more frequent sensor recalibration to ensure accuracy.<sup>62</sup> Sensor insertion and implantation can also result in pain or discomfort, and can pose a risk of infection.

In addition, current CGM devices require calibration against blood glucose values as often as twice a day. As a result, the cost associated with current CGM devices can be high, including the CGM device and sensors as well as consumables for SMBG calibration of the device. Similarly, overall accuracy of current CGM is subject not only to the accuracy of the CGM device, but also the accuracy of the SMBG device used to calibrate it as well as the ability of the individual to use both devices proficiently.<sup>65</sup> Of note is the fact that blood glucose meters are calibrated based on a laboratory reference, but current CGM devices are calibrated against a blood glucose meter, putting them one step away from calibration against a laboratory reference. So, despite the tremendous technological advance that current CGM devices represent, they are not ideal glucose monitoring solutions, which begs the question: what is an ideal solution?

### Toward an Ideal – Non-Invasive Continuous Glucose Monitoring

When asked about the characteristics of an ideal glucose monitor, healthcare professionals and individuals with diabetes often start by stating the device must be non-invasive, non-intrusive and pain-free. It would, of course, accurately monitor glucose levels continuously, warn of impending glycaemic excursions and be small enough to be worn discreetly. So, how would those characteristics translate into a new medical device?

### Accuracy to Support Tight Glycaemic Control Targets

It goes without saying that an ideal glucose monitor must be accurate. The question is: how accurate? Current CGM devices have mean absolute relative differences (MARD) around 13–25 %, <sup>66-70</sup> and a recent study of seven SMBG devices reported MARDs ranging from 6.5–12 %.<sup>71</sup> A non-invasive monitor with a MARD towards the low end or below current CGM devices would certainly offer improvement, and one that approached the MARD of SMBG devices would be closer to ideal. Further, a CGM device that required no user calibration would eliminate one common source of inaccuracy.

### Continuous Information to Drive Optimal Lifestyle, Diet and Treatment

The value of RT-CGM is clear: it provides a complete picture of glucose dynamics over time, including all peaks and valleys, enabling

**Table 1: Overview of Continuous Glucose Monitoring Devices for Home Use on the Market and in Active Development (i.e. those Devices for which a Press Release has been Issued or a Paper has been Published within the Last Two Years)**

Manufacturer	Device	Status	Technology	Sensor Location	Long-Life*	Non-Invasive	Non-Intrusive	Consumable-Free†	Calibration-Free	Accuracy
OrSense Ltd. <sup>4</sup>	NBM 200G CGM	CE Mark (Investigational)	Occlusion spectroscopy	Finger	Yes	Yes	No	Yes	No	13.2 % (MAE) <sup>72</sup>
Abbott Diabetes Care <sup>8</sup>	FreeStyle Navigator CGM	CE Mark, FDA Approval <sup>†</sup>	Electrochemical	Abdomen	No	No	Yes	No	No	12.8 % + 13.6 % (MARD) <sup>88</sup>
Dexcom <sup>c</sup>	SEVEN Plus CGM	CE Mark, FDA Approval	Electrochemical	Abdomen	No	No	Yes	No	No	17 % (MAPD) <sup>67</sup>
Medtronic <sup>o</sup>	Guardian RT CGM	CE Mark, FDA Approval	Electrochemical	Abdomen	No	No	Yes	No	No	19.7 + 18.4 (MAPD) <sup>67</sup>
A. Menarini Diagnostics <sup>e</sup>	GlucoMen Day CGM	Investigational	Microdialysis	Abdomen	No	No	Yes	No	No	10 % (MARE) <sup>73</sup>
C8 MedSensors <sup>f</sup>	HG1-c nCGM	Investigational	Raman spectroscopy	Abdomen	Yes	Yes	Yes	Yes	Yes	Not available
Echo Therapeutics <sup>g</sup>	Symphony tCGM	Investigational	Electrochemical	Abdomen	No	No	Yes	No	No	Not available
CYBIOCARE <sup>h</sup>	PGS	Investigational	Near infrared and physiological	Arm	Yes	Yes	Yes	No	No	Not available
Integrity Applications	GlucoTrack nCGM	Investigational	Ultrasonic, electro-magnetic, thermal	Ear	Yes	Yes	Yes	No	No <sup>3</sup>	25.6 % <sup>74</sup>
Sensors for Medicine & Science <sup>i</sup>	SMSI Glucose Sensor	Investigational	Fluorescence chemistry	Forearm	Yes	No	Yes	No	No	Not available

A. [www.orsense.com](http://www.orsense.com); B. [www.abbottdiabetescare.co.uk](http://www.abbottdiabetescare.co.uk); C. [www.dexcom.com](http://www.dexcom.com); D. [www.medtronicdiabetes.net](http://www.medtronicdiabetes.net); E. [www.menariniidiag.co.uk](http://www.menariniidiag.co.uk); F. [www.c8medsensors.com](http://www.c8medsensors.com); G. [www.echox.com](http://www.echox.com); H. [www.cybiocare.com](http://www.cybiocare.com); I. [www.integrity-app.com](http://www.integrity-app.com); J. [www.s4ms.com](http://www.s4ms.com)  
<sup>†</sup>Sensor life greater or equal to six months. <sup>‡</sup>CGM devices that require calibration via a SMBG device require consumables to support that calibration. <sup>#</sup>Discontinued in the US. <sup>§</sup>Sensor must be calibrated monthly.  
MAE = median absolute error; MAPD = mean absolute per cent difference; MARD = mean absolute relative difference; MARE = mean absolute relative error.

individuals with diabetes and their healthcare teams to maximise euglycaemia. Real-time information can help individuals understand the relationship between lifestyle and dietary choices and their glucose dynamics while retrospective data can help healthcare professionals identify glycaemic patterns and optimise treatment programmes. In addition, real-time monitoring devices can provide customisable alarms that warn of impending hyper- and hypoglycaemia, which will likely ease fear of hypoglycaemia to support implementation of treatment programmes focused on intensive blood glucose control.

**Non-invasive and Non-intrusive to Increase Frequency of Use**

To deliver benefit, CGM devices must be used, preferably about 70 % of the time.<sup>8,49,50</sup> A CGM device with a non-invasive, pain-free sensor that does not require frequent replacement would go a long way towards supporting such frequent use. To be truly non-invasive, the monitor must be a non-in vitro diagnostic device – one that does not require a blood, fluid or tissue sample. Obtaining a sample requires disturbing or penetrating the skin barrier, which is unlikely to be painless or non-intrusive. In addition, because truly non-invasive monitoring would not cause injury or trigger a foreign-body response, it would not be subject to the negative impact those events can have on accuracy.<sup>62,63</sup> Furthermore, many individuals with diabetes have the perception that CGM devices interfere with daily activities.<sup>60</sup> A glucose monitor that could be worn discreetly and be removed when desired without requiring the inconvenience and cost of sensor replacement and recalibration would likely change this perception for the better. In fact, such a device could encourage individuals with diabetes to pursue a wider range of interests since they could keep a close eye on glucose levels throughout most activities.

An ideal glucose monitor, being accurate, continuous, non-invasive and non-intrusive, and having a long-life sensor, would undoubtedly increase the frequency of CGM use and empower individuals to assume more control over their diabetes, improving health and quality of life. Not surprisingly, a number of efforts are underway to develop such a monitor – some closer than others, and some more likely to succeed than others. A larger number of efforts have already come and gone, including the Dream Beam (Futrex Medical Instrumentation Inc.), Diasensor<sup>®</sup> (BICO Inc.), GlucoWatch<sup>®</sup> (Cygnus Inc.) and Pendra<sup>®</sup> (Pendragon Medical Ltd.) CGM devices. Table 1 provides an overview of RT-CGM devices for home use that are actively being developed or already on the market.

**Looking Ahead**

Since the discovery of insulin in 1921, medical technology has continued to improve the management of diabetes as well as make life easier for individuals living with the disease. Before 1975, urine monitoring and a fixed dose of insulin once or twice a day was the general standard of care. Since then, medical advances, such as disposable syringes, laboratory glucose tests, continuous insulin pumps, home-use blood glucose meters and, most recently, continuous glucose monitors, have advanced steadily, with each next-generation product delivering added benefit.

It seems likely that the next step in the advancement of medical technologies for diabetes management will be a non-invasive CGM device that meets some, possibly all, of the characteristics identified by healthcare professionals and individuals with diabetes. Such a

device would support increased adoption and use of CGM, which has been demonstrated repeatedly to reduce risk of long-term diabetes-related complications.<sup>2,3,5</sup> Will a truly non-invasive CGM device be the next technological advance that fundamentally

changes the way diabetes is managed, helping individuals living with the disease achieve that elusive goal of tight glycaemic control? Time will tell, but based on current evidence, the answer seems to be: it very likely will. ■

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