Review Article

Glucose Monitoring Technologies - Complementary or Competitive? Role of Continuous Glucose Monitoring versus Flash Glucose Monitoring versus Self-monitoring of Blood Glucose

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Abstract

We have numerous technologies that can help keep a close watch on an individual's glycaemic status and thereby assist in developing successful diabetes management strategies. For more than five decades, self-monitoring of blood glucose (SMBG) has remained as the gold standard tool to manage glycaemic status and has gained huge acceptance. Rigorous research further led to the development of more and more advanced technologies such as continuous glucose monitoring and flash glucose monitoring. These novel technologies are more promising in terms of revealing the complete glycaemic picture and even more user-friendly than the already established blood glucosemetres. However, they are yet to achieve remarkable accuracy and performance. There will also be a subgroup of patients who will be using these technologies only occasionally and thus will definitely require SMBG at other times. Again, with regard to the retrospective ones, glucose data can be obtained only once they are downloaded to the system and hence, real-time values will still have to be procured with the help of an SMBG. In future when the accuracy and performance of these newer technologies become equal to that of glucometres, the glucometres might vanish. Until then, all these technologies will definitely go hand-in-hand and supplement each other than competing each other. All the related literature were retrieved from various databases including 'PubMed' and 'Cochrane Database of Systematic Reviews' using specific search terms that were relevant to the topics discussed this manuscript.

Keywords: Ambulatory glucose profile, continuous glucose monitoring, diabetes, flash glucose monitoring, glucose monitoring, self-monitoring of blood glucose

Introduction

Several methods for glucose monitoring, each with differing utility and limitations have been available to assess blood glucose levels and for timely management of glycaemic fluctuations. Even though, glycated haemoglobin (HbA1c) is highly accepted for assessing the risk of complications and as a prognosis indicator for the success of treatment of diabetes, it does not capture the 'real-time' information about individual glycaemic excursions. Therefore relying entirely on HbA1c to get a complete picture of glycaemic control is not recommended and frequent monitoring of blood glucose levels to reveal underlying glycaemic variability, should be performed to complement HbA1c.[1] Nowadays, glucose monitoring technologies with varying features and capacities find widespread use in hospitals, outpatient departments, emergency rooms, ambulatory medical care and home self-monitoring, thereby enabling prospective diabetes management. In this review, we have tried to weigh the benefits and shortcomings of currently popular glucose monitoring technologies and tried to assess whether any of them might completely replace the rest in the near future.

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Methodology Adopted for Collecting Literature

All the related literature were retrieved using specific search terms such as 'diabetes', 'glucose monitoring', 'SMBG', 'CGM', 'FGM', 'self-monitoring of blood glucose', 'continuous glucose monitoring', 'flash glucose monitoring', 'ambulatory glucose profile', 'AGP', 'comparison of glucose monitoring technologies', 'advantages of glucose monitoring technologies' and 'disadvantages of glucose monitoring technologies'. Searches were performed in various databases including 'PubMed' and 'Cochrane Database of Systematic Reviews'. All the relevant data were retrieved from these articles and utilised for preparing this review manuscript.

History and Evolution of Glucose Monitoring Systems

Blood glucose meters

The history of glucose monitoring can be traced to mediaeval times and efforts were made to identify various diseases by assessing urine samples. Copper reagent for urine sugar developed by Stanley Benedict in 1908, with several modifications remained the mainstay of urine monitoring of diabetes for more than a century.[2] However, urine tests are unsatisfactory and cannot be used to monitor strict control since they often do not reflect prevailing blood glucose concentrations accurately (urine gets collected in the urinary bladder over a period of several hours and hence does not reflect the glucose levels at the time of testing). In addition, the test gives no information on blood glucose fluctuations below the level of the renal threshold. This is because glucose appears in the urine only when the blood glucose level is above 10 mmol/L and thus, a negative urine glucose test may be obtained either due to normoglycaemia or due to a fatal hypoglycaemic event, making it difficult to differentiate between the two conditions.[3]

Research from Miles-Ames Laboratory became the key element in the history of blood glucosemetres. The quest for a more convenient and specific method led to the development of a 'dip and read' urine reagent strip, Clinistix, in 1957.[4] Later on, Ames research team led by Ernie Adams in 1965 developed the first blood glucose test strip, the Dextrostix, a paper reagent strip.[5] Around the same time, the German company Boehringer Mannheim developed a competitive blood glucose strip, the Chemstrip bG. Limitations associated with these strips further triggered researchers to develop an automatic, electronic glucose test strip reader with improved precision and to yield more quantitative blood glucose results.[6]

In the late 1960s, Ames Reflectance Meter (ARM) [Figure 1] developed by Anton H. Clemens produced quantitative blood glucose results with Dextrostix and was commercially available in 1970.[7] The first reported patient to use blood glucosemetre for his use was Richard Bernstein, who suffered from severe complications of type 1 diabetes mellitus (T1DM). In 1969, he was fortunate enough to procure a glucometre for personal use, through his wife a physician. After endless trials and errors, he could demonstrate that with self-monitoring of blood glucose (SMBG) and subsequent adjustments made in insulin doses, diet and frequency of testing, glucose levels could be normalised and diabetes-associated complications could be minimised. Although he highly accomplished to manage his own disease, as one without medical credentials, he faced difficulties in gaining the necessary attention of the medical community towards his findings. He tried to publish his ideas, but no journal accepted it. Even his physician who was the past president of the American Diabetes Association (ADA) was not convinced. To realise his mission, he left his original profession as an engineer and set out to earn a medical degree. He succeeded in publishing his results and in the early 1980s, ADA changed its position and started to recommend patients for SMBG. Currently, 83 years of age, Bernstein has outlived the life expectancy of a T1DM and his techniques are highly regarded amongst his patients to achieve glycaemic control and to reduce the associated complications.[8]

Figure 1: Earlier and modern-day blood glucose meters; (a) Ames reflectance glucometer (b) modern-day glucometer

Marked evolution in the field during the 1980s led to the development of easier to use, smaller glucometres with built-in memory that could store and retrieve the results. Reagent strips were equipped to accept smaller volumes of blood and some were barcoded to achieve auto calibration and quality assurance.[9] A biosensor is a compact analytical device or unit that incorporates a biological or biologically derived sensitive recognition element integrated or associated with a physiochemical transducer. Clarke and Lyons were the first to describe a glucose biosensor and in 1975 the first commercially successful glucose biosensor using Clark's technology (Yellow Springs Instrument Company analyzer Model 23A YSI analyzer that worked on the principle of amperometric detection of hydrogen peroxide) for the direct measurement of glucose was introduced. The first electrochemical blood glucose monitor for self-monitoring, ExacTech from MediSense Inc., was launched in 1987. It was a pen-sized device and employed glucose dehydrogenase-pyrrole-quinoline quinone enzymes and a ferrocene derivative. Many of the currently available glucose biosensors very much resemble ExacTech meter and various self-monitoring glucose biosensors work on the principle of ferrocene or ferricyanide mediators.[10]

Increased daily frequency of SMBG was significantly associated with lower HbA1c and with fewer acute complications in T1DM children and adolescents.[11] Home blood glucose monitoring is also recommended for T2DM patients to gather information on their glycaemic excursions. To a limited extent, it also helps the patient to adjust the diet and exercise pattern in the day-to-day life. SMBG data also help the physician to individualise the treatment targets as well as empowers the patient to be more conscious towards his diabetes management.[12]

Invention of third-generation glucose biosensors has further paved way to tremendous developments in glucose sensing technology. They are unique from the earlier generation biosensors in the sense that they are reagent-less and are based on direct transfer between the enzyme and the electrode without mediators. This enabled the development of implantable, needle-type devices for continuous *in vivo* monitoring of blood glucose.[10]

Continuous glucose monitoring

Evolution of continuous glucose monitoring (CGM) devices can be traced back to the mid-1970s followed by the development of sensor technology and implantable glucose sensors in early 1980s. However, this technology was not commercially available until the original MiniMed Continuous Glucose Monitoring System (CGMS), CGMS Gold (Medtronic MiniMed, CA, USA) got FDA approval in 1999.[13] Several CGMs, are currently available [Figure 2], that can provide either retrospective or real-time information on glycaemic status.[14]

Suitable candidates for CGM include those with a high degree of glycaemic variability, those with hypoglycaemic unawareness, shift workers, patients who use insulin pumps, athletes, and women who are planning to become or are pregnant. Compatibility of certain CGMs with insulin delivery devices has also made it possible to achieve the aim of closing the loop. In trials such as STAR-1, STAR-3 and DirecNet, CGM use brought about improvements in HbA1c with simultaneous reductions in the frequency and severity of hypoglycaemia in T1DM children and in adults with T1DM or T2DM.[15-18] CGMs also helps improve diabetes control by lowering hypoglycaemia risk, which is of particular value to patients with hypoglycaemia unawareness. Meanwhile, retrospective analysis enables clinicians to discriminate between traditional hyperglycaemia and rebounds from hypoglycaemia.[19,20]

Figure 2: Continuous Glucose Monitoring System (iPro2)

The sensor measures the interstitial fluid (ISF) glucose where a lag is noted with the sensor glucose levels when compared to blood glucose levels due to the physiologic delay in transferring glucose between the blood and ISF space, the transit time of ISF glucose through the sensor membrane and signal filtering. Therefore, CGM readings cannot be considered 100% accurate.[21] Besides, the glucose sensor must be frequently calibrated against corresponding blood glucosemetre values to overcome signal drift issues and to ensure the continuous accuracy of sensor data and the calibration should be preferably be performed only during the times when the blood sugars are most stable.[21,22]

Ambulatory glucose profile and flash glucose monitoring

Ambulatory glucose profile (AGP) is a modal graph where 14 days of glucose data are collated to form a graph as if they occurred in a single 24-h period. The collated data also helps to predict the glucose pattern for the next 30 days, enabling us to visualise glycaemic patterns. The history of AGP dates back to 1987, where Mazze *et al*. used reflectance meters containing memory chips to store 440 individual blood glucose values with corresponding time and date. These data were organised into 14 day periods and collapsed into a graphical depiction which came to be known as AGP. Thus, AGP was a novel step which systematically presented SMBG data and reflected features beyond glycaemic control including amplitude and frequency of changes in the glycaemic level. However, this technology was wrought by several limitations including that AGP being a daytime profile and not a continuous monitoring system. It did not consider variables including diet, exercise, the timing of medications, etc. Moreover, frequent and sustained SMBG was required for the construction of AGP.[23] Interest on AGP rekindled when an expert panel of diabetes specialists met in Florida, to discuss the utility of CGM in clinical practice and research applications where they were introduced to the universal software report, the AGP, created by Mazze *et al*., and further developed by the International Diabetes Center,[24] Minneapolis, MN. The panel observed that standardising glucose reporting and analysis, with tools such as AGP, maybe one step towards optimising clinical decision making in diabetes.

Abbott launched the FreeStyle Libre 'flash glucose monitoring' (FGM) in Europe in the year 2013 and its professional version FreeStyle Libre Pro (FSLP) system in India [Figure 3], in March 2015. It is basically a modified version of a conventional CGM and comes with more advanced features such as being readily available in a factory calibrated

Figure 3: Flash Glucose Monitoring (FreeStyle Libre Pro)

mode which eliminates frequent finger-prick calibrations, gives more stable glucose measurements (capturing up to 1340 glucose results), increased sensor wear-time of 14 days and requires no patient interaction.[25] The FSLP software makes use of AGP reporting to obtain an automated and standardised visualisation of glucose data so as to apprehend when the most variability is occurring and thus take necessary precautions.[26,27] Performance, accuracy and acceptability of FSLP have been proven in T1DM children[28,29] as well as in adults with T1DM and T2DM.[30,31]

Will Novel Glucose Monitoring Systems Replace Self-monitoring of Blood Glucose?

With the benefits of SMBG in the prevention of long-term complications of diabetes, this procedure should be recommended by health-care professionals in all patients with diabetes irrespective of the medications. However, the beneficial effects can be perceived only by those individuals in whom therapeutic and lifestyle changes are incorporated based on monitored parameters.[12] For such changes to be made, either the patient should be highly educated and motivated or should receive directions from experts at frequent intervals. Another major drawback of SMBG is its ineffectiveness in detecting asymptomatic hypoglycaemia or nocturnal hypoglycaemia, especially in the presence of near-normal HbA1c values.[32] Since it provides information only about the blood glucose at a particular point, significant glycaemic excursions may often go unnoticed.

In contrast, CGM and FGM systems share many remarkable features, and more importantly, can effectively reveal glycaemic trends. The glucose data procured by these systems serve as a valuable learning tool, showing patients the immediate impact of lifestyle and medicinal decisions. In real-time versions, responding in a timely manner to high and low glucose alerts can reduce glucose variability. However, more randomised controlled trials are required to prove the superiority of CGM and FGM over SMBG. Furthermore, there is a sub-group of patients (especially T2DM patients) who will not be using these novel technologies continuously and thus will definitely have to perform SMBG at other times. With regard to the retrospective ones, the glucose data can be procured only once they are downloaded to the system and hence, real-time values will still have to be obtained by performing SMBG. Similarly, though these technologies provide huge data, to reap the real advantage of it, these data need to be analysed and interpreted which requires a lot of time and commitment both from the side of the patients and that of the physicians involving multiple members from either side. This is not practically possible in all the settings. On the contrary, glucometers are easy to use. A major limitation of glucometers, i.e., pain of pricking the finger, which is still a concern for around 60% of the patients, is going to go away with new innovations that avoid the pain of pricking the finger.

Some evidence is available that support the use of CGM over SMBG in the T1DM paediatric population.[16] However, many failed to show the effectiveness of CGM in reducing HbA1c in this group.[33] Few studies have proven the effectiveness of CGM in type 2 diabetes patients over SMBG.[34] The lag time associated with CGM, its short sensor wear time (3-7 days) and need for frequent finger-prick calibration stands as major limitations of this technology.[35] Even though a CGM produces far more information than a normal SMBG, it measures glucose in ISF and not blood. Therefore a discrepancy should be expected between the values obtained from CGM and SMBG, more particularly at the times when glucose fluctuations are prominent such as during a meal or exercise. Considering this fact, the decision of administering insulin or correcting hypoglycaemia should be done only based on SMBG and not on the values from CGM. Frequent calibration of the CGM system should be performed on the basis of SMBG readings (1–3 times a day) which is another reason why CGMs cannot completely replace SMBG. Similarly, even with improved performance standards, the accuracy and reliability of CGM systems might get compromised during exogenous pharmacologic interferences. In one of the studies by Ananda *et al.*, the CGM detected glucose values were found to vary due to interference from acetaminophen whereas plasma glucose concentrations remained unaltered.[36]

Benefits of wearing a CGM sensor seem to vary according to the duration and frequency of its use. STAR 3 study revealed that when CGM was worn 60% of the time, HbA1c was lowered by 0.5% in contrast to 1.2% drop achievable when it was worn 80%–100% of the time.[37] The 'hassle factor' associated with CGM such as the need for frequent needle insertions, sensor and transmitter (or recorder) to be worn throughout, getting exhausted from responding to cautionary, redundant, or outright false alarms, etc. all poses inconveniences, physical discomforts, and psychological burdens to the users.[14] Cost is another major prohibiting factor towards the use of CGM or FGM. The majority of the health plans, insurance companies and governments in most countries throughout the world do not cover for these technologies. In many of the instances, depending on the patient's interest and their financial resources, some patients might opt for these technologies only briefly or intermittently as a diagnostic, educational and/or motivational tool, rather than a core aspect of daily diabetes management.[14] Some of the limitations of CGM such as short sensor lifetime, need for finger-prick calibration, etc. has been resolved to a considerable extent by Abbott's FreeStyle Libre FGM.[38] However, the manufacturer itself in the product description has indicated a caution that the device may at times inaccurately indicate hypoglycaemia[39] and thus necessitates SMBG whenever such a scenario arises. A general comparison of the benefits and shortcomings of SMBG, CGM and FGM are provided in Table 1.

Numerous options for glucose monitoring available as of today have their own advantages and disadvantages. The ultimate goal of any approach should be to achieve adequate glycaemic control by avoiding hypoglycaemia and with utilisation of available resources of monitoring.[40] With current evidence, both CGM and FGM systems may be used as a technology only to supplement the use of SMBG in the management of diabetes. Newer technologies might replace the old ones, but this is not likely to happen at least for the next 10 years. Some of the drawbacks/limitations of novel CGMs that could be pointed out to argue that they will not likely replace SMBG in near future are listed in Table 2.

Conclusion

SMBG remains the gold standard of blood glucose monitoring and its usefulness to ward off diabetes complications is very well-accepted. Newer devices such as CGM and FGM systems have further improved the prospects of glucose monitoring and provide more insights into the trends and patterns of glycaemic variations. However, in the current scenario, these novel technologies may not completely overshadow SMBG. The associated costs, the discrepancy with the blood glucometer values especially during pronounced glycaemic excursions, shorter sensor wear-time, etc. still poses as the shortcomings of these devices. Technologies are going to be complementary, with the SMBG, CGM and FGM technologies complementing each other, especially in the current era of a patient-centred approach where the physicians need to choose which all tests need to be employed either alone or in combination for a successful diabetes management. Patients will use CGM along with insulin pumps and Artificial Pancreas, many others will employ FGM sensors for real-time or retrospective glucose monitoring. Whatever be the purpose, there is the need for a strong and committed team of physicians, dieticians and others who can help patients with changing therapies and behaviours. Therefore, none of these patients will probably be using these glucose sensors all the time and majority of the time they will be using glucometres.

Another domain that is vastly being explored is that of non-invasive glucose monitoring technologies. The major advantages of such technologies are that they can eliminate the painful pricking experience, risk of infection, and damage to finger tissue. Although this non-invasive concept was launched more than 30 years ago, it is still in its infancy. The different techniques/technologies that are being extensively explored include Bioimpedance spectroscopy, electromagnetic sensing, fluorescence technology, mid-infrared spectroscopy, near infrared spectroscopy, optical coherence tomography, optical polarimetry, raman spectroscopy, reverse iontophoresis, ultrasound technology, etc.[41] Many devices that are based on the aforementioned technologies are available and most of them require nothing more than placing a finger on or in a sensor. For instance, GlucoWise is a U-shaped sensor which can fit the corner of the hand between thumb and forefinger. Similarly, GlucoTrack can be attached to the ear lobe and uses a unique and patented combination of 3 different technologies: ultrasound, electromagnetic and thermal, brought together by a proprietary algorithm. I-SugarX works on the principle that it can measure the fluorescence of glucose in the aqueous solution of the eye. Most of these devices can also be linked

Table 1: General comparison of the benefits and shortcomings of self-monitoring of blood glucose, continuous glucose monitoring and flash glucose monitoring

Features	SMBG	CGM	FGM
Time since being used	Time tested	Relatively new (approximately 15 years)	Very new (approximately 2 years)
Costs involved	Cheaper	Relatively expensive	Relatively cheaper
Accuracy	Very accurate	Better with newer sensors	Relatively accurate
Source of glucose measurement	Blood	ISF	ISF
Requirement of finger pricks	Always required	Required for calibration	Not required and hence virtually painless
Need of the device being attached to the body	No device attached to the body	Relatively big sensor attached to the body	Tiny sensor but still attached to the body
Volume of glucose data obtained	Provides a single glucose reading	Provides the glucose trend over several days (gives reading every 5 min for 5-7 days)	In addition to CGM, provides an AGP (gives reading every 15 min for 14 days)
Possible to access GV	Difficult	Yes	Yes
Level of motivation required	High	Moderate	Minimal
Level of subject interference required	Maximal	Moderate	Minimal and hence can capture glucose values of even those subjects who are not at all motivated

SMBG: Self-monitoring of blood glucose, CGM: Continuous glucose monitoring, FGM: Flash glucose monitoring, ISF: Interstitial fluid, AGP: Ambulatory glucose profile, GV: Glycemic variability

Table 2: Drawbacks/limitations of novel continuous glucose monitoring systems

- Glucometer measures blood glucose whereas CGMs measures glucose in the ISF. Thus the accuracy of CGM sensors will never be the same as blood glucometers and periodic calibration (except FreeStyle Libre sensors that comes in a pre-calibrated mode) will have to be done using blood glucometers
- Analysis and interpretation of huge data acquired by the CGM and FGM systems are bothersome at least to a subset of the users since they demand a lot of time and commitment involving multiple members from both patient's and physician's side, which is practically impossible in many of the cases. The majority of the users hence will still opt for glucometers due to its virtue of simplicity
- Both CGM and FGM have only a short sensor wear time in the range of 7-14 days and the patterns of predicted glucose data pronouncedly vary depending on the period of sensor use. Thus for the ultimate understanding of glycemic status, one would definitely have to rely on SMBG
- Discrepancies are noted in the glucose values obtained from CGM and FGM, more particularly at the times when glucose fluctuations are prominent such as during a meal or exercise. Therefore the decision of administering insulin or correcting hypoglycemia should be done only based on SMBG and not on the values from CGM
- Even for those individuals who are using the CGM or FGM sensors, they may not be using the sensors continuously. Therefore, when they are not on a sensor, they will definitely have to depend on glucose meters to address their diabetes

CGM: Continuous glucose monitoring, ISF: Interstitial fluid, FGM: Flash glucose monitoring, SMBG: Self-monitoring of blood glucose

to a smartphone or a personal computer and thus allows the user to store data in the cloud.[42,43]

Guidelines will probably emerge regarding the recommended frequency of use of each of these technologies. Glucometers are already proven cost effective. Similarly, it needs to be proven that these newer devices are extremely accurate as well as cost effective in terms of preventing the cost of complications in diabetes. To address the inconvenience of painful finger pricks associated with SMBG, patient education regarding less painful techniques. alternative testing sites such as the forearm may be promoted.[44] Whatever be the mode of glycaemic monitoring, beneficial effects of these technologies can only be perceived, if the individuals are compliant to diabetes care and are ready to bring in therapeutic and lifestyle changes based on the procured data.

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