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Continuous Glucose Monitoring (CGM) Technology: Current Challenges and Future Promises for a Better Diabetic Lifestyle

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ABSTRACT

Continuous Glucose Monitoring (CGM) is a relatively new technology which has the potential to assist people living with type 1 or type 2 diabetes and treated with insulin to achieve the goal of optimum control of blood glucose. Devices for continuous glucose monitoring (CGM) are currently a major focus of research in diabetes management. It is envisioned that such devices will have the ability to alert a diabetes patient of impending hypoglycemic/ hyperglycemic events and thereby enable the patient to avoid extreme hypoglycemic/ hyperglycemic excursions as well as minimize deviations outside the normal glucose range, thus preventing both life-threatening events and the debilitating complications associated with diabetes. It is anticipated that CGM devices will utilize constant feedback of analytical information from a glucose sensor to activate an insulin delivery pump. Depending on whether the CGM device penetrates/breaks the skin and/or the sample is measured extracorporeally, these devices can be categorized as totally invasive, minimally invasive, and non-invasive. However, at present, most of these technologies are plagued by a variety of issues that affect their accuracy and long-term performance. Considering the advantages and some of the disadvantages of this technology and comments on it from the point of view of a health professional working in a resource limited setting. In the final analysis, judgements as to its usefulness will be based not only on its effectiveness but also its cost effectiveness. This article presents the components, working and benefits of existing CGM technologies, highlighting critical aspects of its use and importance in diabetes and many clinical settings.

INTRODUCTION

Diabetes often referred to by doctors as diabetes mellitus, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin or both. For people with Type 1 Diabetes or Diabetes Insipidus: Patients body does not produce insulin and for people with Type 2 Diabetes or Diabetes Mellitus. The body does not produce enough insulin for proper function, or the cells in the body do not react to insulin (insulin resistance). Gestational Diabetes is a type that affects females during pregnancy, as women have very high levels of glucose in their blood, and their bodies are unable to produce enough insulin to transport all the glucose into their cells, resulting in progressively rising levels of glucose. In 2013, it was estimated that over 382 million people throughout the world had diabetes. The most common diabetes symptoms include frequent urination, intense thirst and hunger, weight gain, unusual weight loss, fatigue, cuts and bruises that do not heal male sexual dysfunction, numbness and tingling in hands and feet. Approximately 90% of all cases of diabetes worldwide are of type 2. If you have Type 1 and follow a healthy eating plan, do adequate exercise, and take insulin, you can lead a normal life. Type 2 patients need to eat healthily, be physically active and test their blood glucose. They may also need to take oral medication, and/or insulin to control blood glucose levels. As the risk of cardiovascular disease is much higher for a diabetic, it is crucial that blood pressure and cholesterol levels are monitored regularly. As suggested by the Diabetes Control and Complications Trial report, complications arising from diabetes can be reduced and even prevented via careful management that includes regular checking of glucose levels. It is recommended that a T1DM patient should check his/her glucose levels at least four times per day, while a T2DM patient should check his/her glucose levels at least two times per day. For this, at present, most diabetes patients rely on glucose strips along with handheld glucose meters that record glucose levels in blood drawn via finger pricking, i.e., self-monitoring of blood glucose (SMBG). However, the pain associated with finger pricking together with the inability of test strips to reflect the overall trend in the glucose level of individual patients, i.e., the direction and the pattern associated with the patients daily habits, renders user-independent continuous glucose monitoring (CGM) a highly desirable proposition. Use of CGM devices will enable the identification of glucose trends, thereby assisting physicians in optimizing treatment plans and facilitating appropriate clinical decisions in cases of emergency. In addition, theoretical modelling has predicted that an additional 5 years of life, 8 years of sight, 6 years free from

kidney disease, and 6 years free from amputations can be gained by a diabetes patient who follows tight CGM glucose control versus the standard SMBG.

MATERIALS AND METHODS

Mechanism of CGM Technology:

CGM is a way to measure glucose levels in real-time throughout the day and night. A tiny electrode called a glucose sensor is inserted under the skin to measure glucose levels in tissue fluid. It is connected to a transmitter that sends the information via wireless radio frequency to a monitoring and display device.

Fig. 1. Tracking blood glucose level on an iOS device through the Dexcom G5 Mobile transmitter.

Components of a CGM device:

A CGM device typically consists of (*i*) a glucose sensor that continuously measures physiological (blood or interstitial fluid [ISF]) glucose levels, (*ii*) an electronic processing unit that is in communication (wired or wireless) with the glucose sensor, and (*iii*) a data display unit. These data may then be used to determine whether the patient requires insulin. In futuristic closed-loop CGM systems, in addition to the for mentioned components, an insulin delivery unit and possibly a glucagon delivery unit will be incorporated. Through a patient-specific algorithm, the correct dosing of insulin or glucagon will be provided to the patient via feedback from the electronic processing units.

Glucose sensors:

Placement of the glucose sensor (whether it penetrates the skin or not) and its communication with the electronic processing unit defines the invasiveness of a CGM device. On this basis, CGM devices can be classified into three categories: (1) invasive (totally implantable) sensors, (2) minimally invasive sensors, and (3) non-invasive sensors.

Detection of Glucose Methodologies:

Glucose detection using electrochemical-based methods can be broadly categorized under enzymatic and non-enzymatic approaches. Typically, the glucose- specific enzyme [glucose oxidase (GO_x)] catalyses the oxidation of glucose to gluconolactone. In this process, the enzyme (i.e., the enzyme's redox cofactor, flavin adenine mononucleotide) is converted to its reduced form (flavin adenine dinucleotide). Glucose detection based on optical approaches can be broadly classified as (1) fluorophore-based and (2) direct (nonfluorophore)-based techniques. The fluorophore-based approaches utilize an affinity sensor principle wherein glucose and a fluorophore bind competitively with a receptor that is site specific to both ligands. Nonfluorophore-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.

Continuous glucose monitoring (CGM) provides a continuous measure of interstitial glucose levels, a complete pattern of glucose excursions, real time alarms for thresholds and prediction of hypo and hyper glycaemia as well as rate of change alarms for rapid glycaemic excursions. For CGM users, there is a significant improvement in blood glucose control without increasing the risk of hypoglycaemia. For people with type 1 diabetes using either multiple daily injections (MDI) or insulin pumps, CGM is very useful in improving glycaemic control without increasing the risks of severe hypoglycaemia.

Fig. 2. A typical blood glucose monitoring device from Dexcom using CGM Technology.

Role of CGM in various clinical settings:

CGM use has also been effective in other settings such as ICU (to maintain acceptable blood glucose targets for critically ill patients); infants (having cardio-respiratory bypass surgery); new born infants at risk for neonatal hypoglycaemia; patients with cystic fibrosis who are at risk of developing cystic fibrosis related diabetes (CFRD); and monitoring patients with glycogen storage disorders specifically when combined with urine ketone and/or blood lactate measurements.

Factors affecting the reliability on CGM Devices:

1. Accuracy:

As with any other analytical medical device, accuracy forms the most important requirement of a CGM device. Accuracy in CGM devices is required not only to transition these from stand-alone continuous sensing devices to "closed-loop" artificial pancreas but also to increase confidence among patients and physicians.

At present, there is no consensus on the criteria to be used for evaluation of CGM device performance. Most of the existing methods include comparing values obtained from the CGM device against corresponding reference values using linear regression analysis, error grid analysis, predicted error sum of squares, and mean absolute deviation.

2. Calibration:

A CGM device contains various components, all of which are potential sources of error. Currently, external glucose measuring devices are used to calibrate CGM devices to ensure accuracy. However, this type of calibration may not be ideal.

3. Selectivity:

Selectivity of a CGM device corresponds to its ability to respond only to changes in glucose within the pool of metabolites present in the body. However, there are many molecules with electrochemical and/or optical signature similar to *D*-glucose (the biologically active form), which renders selectivity of a sensor a major obstacle to CGM devices. Some of these problems can be solved by developing more sensitive and stable instrumentation.

In resource limited settings, where access to diagnosis, monitoring and treatment is a challenge, the use of CGM has its own limitations where the practical issues may result in these devices being more of a burden than a benefit.

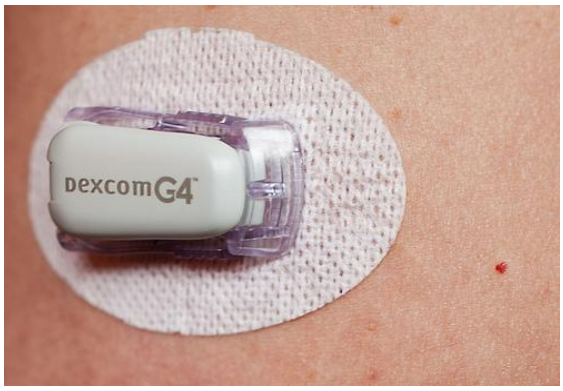

Fig. 3. A typical Dexcom G4 Sensor and Transmitter attached at the lower abdominal area.

RESULTS

In the STAR 3 study, wherein 485 subjects switched from MDI and routine blood glucose testing to CGM, there was a significant improvement in HbA1c without an increase in frequency of severe hypoglycaemia or diabetes ketoacidosis (DKA) in both adults and children.

DISCUSSION

Continuous Glucose Monitoring Technology is a revolutionary and innovative advancement in the continual process of monitoring blood glucose levels in the body. This technology from Dexcom got FDA clearance on 21st July 2016. Proper education and well satisfactory marketing with affordable pricing will help in the ease of acceptance of this technology by millions of diabetics around the globe in healthy and regular monitoring of their blood glucose levels. From the perspective of the person with type 1 or type 2 diabetes, major barriers are awareness, cost, supply of usable equipment and technology. There is evidence that many people with diabetes reduce their frequency of self-monitoring of blood glucose (SMBG) after starting on CGM. In addition, towards the end of sensor life, the accuracy of the device is questionable and thus SMBG is still a necessary measure at regular intervals to make treatment decisions, calibrate the device and confirm any unusual CGM values. In an environment where most people with diabetes have limited access to even basic commodities

such as insulin, syringes, monitoring devices and education, the introduction of CGM devices is still a distant dream except for the privileged few. In many circumstances, insulin is used for sheer survival rather than adequate blood glucose control.

Future studies should aim to correlate implant size and sensor coatings to various interrelated factors such as immunogenicity, cytotoxicity, genotoxicity, tissue sensitization and irritation, intracutaneous reactivity, hemocompatibility, chronic toxicity, and biodegradation. In order to tackle all the aforementioned factors, advanced CGM device architectures together with multiple strategies from multidisciplinary research involving chemists, material scientists, engineers, pharmacists, and physicians are needed. Given enough time and resources, the confidence level is high that an *ideal CGM device* is within reach.

Fig. 4. Ease of daily blood glucose monitoring with a CGM Device i.e., Dexcom G5 Mobile using CGM Technology.

CONCLUSION

In conclusion, critical evaluation of various CGM technologies must not only focus on a given advantage afforded by a certain technology but rather holistically evaluate various physicochemical and physiological aspects that are closely linked to device performance and the lifestyle of the patient. Considering the challenges of CGM device availability, affordability and safety, CGM Technology mediated devices need more attention to raise the standards for the same. If so done, an additional 5 years of life, 8 years of sight, 6 years free from kidney disease, and 6 years free from amputations can be gained by a diabetes patient who follows tight CGM glucose control versus the standard SMBG.

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