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# CONTINUOUS GLUCOSE MONITORING DEVICES: A SYSTEMATIC REVIEW

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**ABSTRACT**

Continuous glucose monitoring (CGM) is an increasingly adopted technology for insulin-requiring patients that provides insights into glycemic fluctuations. CGM can assist patients in managing their diabetes with lifestyle and medication adjustments. This article provides an overview of the technical and clinical features of CGM based on recently approved devices, i.e., from June 2018. A detailed description is presented of three professional (retrospective), three personal (real-time) continuous glucose monitors, and three sensor integrated pumps (consisting of a sensor and pump that communicate with each other to determine an optimal insulin dose and adjust the delivery of insulin) that are currently available in the United States. Outpatient CGM Outcomes, focusing on haemoglobin A1c (HbA1c), hypoglycemia, and quality of life. Issues affecting accuracy, detection of glycemic variability, strategies for optimal use, as well as cybersecurity and future directions for sensor design and use are discussed. In conclusion, CMG is an essential tool for monitoring diabetes that has been shown to improve outcomes in patients with type 1 diabetes mellitus. Given currently available data and technological developments, we believe that with appropriate patient education, CGM can also be considered for other patient populations.

## INTRODUCTION

Continuous glucose monitoring (CGM) is an increasingly adopted technology for insulin-requiring patients. CGM uniquely provides insights into glycemia that assist patients in managing their diabetes with appropriate lifestyle and medication adjustments. This article provides an overview of the technical aspects and clinical considerations for using continuous glucose monitoring. In 2014, the global cost of diabetes, calculated in International Dollars, was $825B/year taking into account the cost of treating diabetes mellitus plus managing the disease and its complications. If current trends continue with a new diagnosis of diabetes, it is estimated that over 700 million adults worldwide would be affected by diabetes by 2025.1. A vast majority of patients with Diabetes does end up receiving chronic disease treatment in the form of insulin therapy to help control their blood sugars in conjunction with a blood glucose meter. Without adequate blood sugar control, diabetes can lead to many debilitating and life-threatening conditions such as heart disease, stroke, vision loss, kidney disease, amputations, and ultimately death. To prevent these conditions from occurring, patients with diabetes are strongly encouraged to make dietary changes and frequently monitor their blood glucose.2. To receive the appropriate dose of insulin, an accurate measurement of blood glucose is required, typically with a finger- prick glucose meter. However, patients continue to struggle with the pain associated

with finger-pricks before injecting insulin. With the introduction and advances with continuous glucose monitors (CGMs), the less than ideal compliance of self-monitoring of this disease may be coming to an end.

## HISTORY OF DIABETES MANAGEMENT:

Dating as far back as 1552 B.C., the existence of diabetes and its symptoms were reported, with the earliest documentation found on a 3rd Dynasty Egyptian papyrus by a physician named Hesy-Ra. He reported symptoms his patients presented with, such as frequent urination. The very first way of studying diabetes mellitus was through the examination of the urine. There were several chemical tests developed with various reagents, primarily indicating if there was any sort of sugar present in the urine. Unfortunately, a diagnosis of diabetes through the analysis of the urine often meant that death was rapidly approaching. If there was a sugar present in the urine, the only intervention known at the time was changing one's diet, which was often too late to alter the course of their disease. In 1923, Eli Lilly and Company began the commercial production of what is known today as "insulin".3.In the early part of the 20th century, a physician by the name of Dr Frederick Allen counselled patients to maintain a low-calorie diet, which allowed for patients with diabetes to extend their lives for about a year or so.4, 5. As this medical breakthrough of pancreas extract began to spread across the nation, there still was a need to measure a patient's blood glucose value before the injection of "insulin." Without having an accurate measurement of the patient's level of sugar, injecting insulin could pose more of a risk to the patient rather than a benefit by inducing hypoglycemia. By 1925, home testing for sugar in the urine was introduced, which involved the process of eight drops of the patient's urine in being mixed in a test tube with six c.c of Benedict's solution, all components of which were dispensed by a physician at the time. The instructions required that the test tube is placed in boiling water for several minutes and depending on the colour change observed, the patient would know their sugar level (Fig. 1). Green represented light sugar in the urine, yellow represented moderate sugar, and red/orange presented heavy sugar. The executives of Miles Laboratories' wished to join the prescription drug business with their new biochemistry division and were optimistic about finding the "wonder drug." Alfred Free understood the current home method of analysing urine for sugar and knew there was room for advancement because it was nonspecific, detecting all forms of sugar, not just glucose. Helen Free felt that this limitation would cause some hesitation by doctors to use this system, and she concluded this field of study had the potential to be a niche for Miles Laboratories.6. The research of diabetes continued to expand by refining insulin and the monitoring system. By the late 19400s, Helen Free developed the "dip-and-read" urine test known as Clinistix, which was capable of monitoring urine glucose levels virtually instantaneously. Free's team was able to embed the reagents on a filter paper strip comprising the first test specific for glucose, with the release in 1956. This advancement used a double sequential enzymatic reaction via glucose oxidase, peroxidase, and orthotolidine. In this reaction, glucose oxidase catalysed the oxidation of glucose to gluconic acid while also converting oxygen to hydrogen peroxide. With a peroxidase, the hydrogen peroxide was used for the oxidation of orthotoluidine into a deep blue chromogen, which was the visual indicator of glucose level (Fig. 2).7. Alterations were made to this extensive process, and in 1964, another test came to the market by the name of Combur-Test, made by Boehringer Mannheim. This test was sensitive towards glucose, protein, pH of urine, and even extended to include ketones later in the product known as Ketostix/ Ketodiastix. Although the urine "dipstix" tests

on the market were painless and low cost, some glaring limitations existed, such as the inconvenience due to the requirement of urine, and the test itself appeared "dirty" and/or having poor hygiene.8.

## CONTINUOUS GLUCOSE MONITORING SYSTEMS:

As of 1999, a new era in diabetes care began as the first-ever continuous glucose monitoring (CGM) system was approved to help people being diagnosed with diabetes.9. The development of this new technology allowed patients to monitor their blood sugars by inserting a device subcutaneously. The CGM system measures a patient's glucose levels in their interstitial fluid over the entire day. For patients with Type I diabetes, it is recommended to have four blood glucose readings per day. With CGMs, instead of the four readings per day, patients and medical providers now have a more in-depth knowledge of the fluctuations each unique patient experiences throughout their day. The sensor component of the continuous glucose monitoring system is capable of taking measurements every 5 min. With this extensive data, medical providers can make long-term adjustments in drug therapy unique to every patient's lifestyle.10. Another added benefit of CGM's is the detection of hypo and hyperglycemia. The most current devices now send alert signals to patients when their blood glucose falls out of the acceptable range.

The extremes of hypo- and hyperglycemia are known to put a patient with diabetes at higher risk of stroke, vision loss, kidney disease, amputations, and even death. Being able to prevent these complications from occurring with CGM can improve the quality of life of the patient and reduce the cost burden of diabetes on the U.S. healthcare system. CGM was included in the 2015 American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (AEC) – Clinical practice guidelines for developing. A diabetes mellitus comprehensive care plan. It stated that CGM should be considered for patients with Type I and II diabetes on basal-bolus therapy to improve A1C levels and reduce the chances of experiencing hypoglycemia. This statement presented in the guidelines had a level of evidence of grade b; bEl 2, which signifies a standard recommendation with moderate evidence that supports the claim.11. Since the advent of CGM, challenges they have faced have been a lag time as well as accuracy. However, significant advancements have been made since 1999, with improved versatility, new indications, and higher accuracy.

## KEY PLAYERS WITHIN THE CGM INDUSTRY:

There have been multiple medical device products for CGM that have received pre-market approval (PMA) by the FDA since 1999. The three medical device companies that have been the main competitors in this industry are Abbott Laboratories, Medtronic, and Dexcom Inc. Abbott Laboratories is a worldwide health care company that focuses on generic drug manufacturing, medical devices, diagnostics, and nutritional products. Abbott works on a variety of medical devices and holds a separate division for diabetes care, where they have launched multiple glucose monitoring devices. To date, Abbott has launched glucose monitoring devices known as the Freestyle blood glucose meters (Freedom Lite, InsulinX, Lite, and Precision Neo) that are commonly prescribed by providers and dispensed at retail pharmacy settings.12. In terms of continuous glucose monitoring, the two products released have been the Freestyle Navigator continuous glucose monitor in 2008 and the Freestyle Libre Pro Flash glucose monitoring system in 2016. In 2015, it was reported that Abbott Laboratories' total revenue was 20.4 billion dollars. 13. According to FY2016 data, the business revenue for their diabetes group was

1.8 billion dollars, which was roughly 6% of their total business revenue.14.

Finally, Dexcom Inc. is a U.S. based company that works solely on the development, manufacturing, and distribution of continuous glucose monitoring systems for diabetes management worldwide. Their first CGM technology was launched in 2006, called the Dexcom STS Continuous Monitor. Most recently, the company launched its G5 platform that is compatible with Android cellular devices. Dexcom's G4 Platinum Continuous glucose monitoring system also received FDA approval for expanding its indication for the pediatric population, ages two years old to 18 years old.15. Along with Medtronic, Dexcom has made a non-exclusive agreement with Tandem Diabetes care for the market of compatible insulin pumps for the G5 and future G6 systems.16. In 2015, Dexcom's total revenue was $402.0 million for the fiscal year.17.

**RECENTLY APPROVED DEVICES:**

**A. MINIMED 670G SYSTEM – P160017/S031**

**Product Name**: Minimed 670G System

**PMA Applicant**: Medtronic MiniMed, Inc. 18000 Devonshire Street, Northridge, CA, 91325

**Approval Date**: June 21, 2018

It is the first FDA approved hybrid closed loop system that monitors glucose and automatically adjusts the delivery of long-acting or basal insulin. It should be used in persons aged 14 years and older. It measures the users' glucose levels for up to 7days, an insulin pump that delivers insulin to the user, and a glucose meter used to calibrate the CGM. This system has two modes: Manual & Auto mode.

**Cautions**

- This device may not be safe in children under seven years.
- People who require less than the total insulin dose of 8units per day because the device requires a minimum of 8 units per day to operate safely.
- This device should not be used in people whose vision or hearing does not allow recognition of the pump signals and alarms.
- Patients should not expose their pump to a magnet, such as pump cases that have a magnetic clasp.


**Fig.3. Minimed 670G System – P160017/S031**

**Sources of the image:** Minimed 670G System - P160017/S031 [Internet]. U.S. Food and Drug Administration.

**B.T: SLIM X2 INSULIN PUMP WITH BASAL IQ TECHNOLOGY – P180008**

**Product name**: t: slim X2 Insulin Pump with Basal – IQ technology

**PMA Applicant**: Tandem Diabetes Care, Inc. 11045 Roselle Street Suite 200, San Diego, CA 92121

**Approval Date**: June 21, 2018

This system is intended to monitor glucose levels and deliver insulin for the management of diabetes. It works by measuring glucose levels and automatically adjusts insulin delivery by either administering or withholding insulin. This system is intended for single patient use, requires a prescription, and is intended for use with NovoLog or Humalog U-100 insulin.

**Cautions:**

- It should not be used in patients whose vision or hearing does not allow the user to recognize system alerts.
- Patients should not expose their sensor to MRI equipment, CT scans, or other

types of radiation. Exposure may cause the device to malfunction.

- If exposed to them, discontinue the use of the device.


**Fig.4. T: slim x2 insulin pump with basal IQ technology – p180008**

**Sources of the image:** t: slim X2 Insulin Pump with Basal-IQ Technology - P180008 [Internet]. U.S. Food and Drug Administration.

**C.FREESTYLE LIBRE 14DAY FLASH GLUCOSE MONITORING SYSTEM – P160030/S017**

**Product Name**: Freestyle Libre Flash Glucose Monitoring System

**PMA Applicant**: Abott Diabetes Care, Inc. 1360 South Loop Road, Alameda, CA, 94502

**Approval Date**: July 23, 2018

It is a glucose monitoring system used by adult patients without obtaining a blood sample from the fingertip. This supplement updates the Freestyle Libre's approval to provide on-demand glucose information to a user for up to 14days. This sensor has to be applied to the back of the person's upper arm, where the electrical signal was generated. The generated electrical signal is converted into a blood glucose reading & transmitted to a dedicated mobile device (reader). It should be used in persons aged 18years and older.

**Cautions**:-

- It must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan. The exposures from the above tests may damage the sensor and could cause incorrect readings.
- This system is not approved for pregnant women, dialysis persons, or critically ill patients.
- It is not used for dehydrated patients, hypotensive patients, shock patients.


**Fig. 5. Freestyle libre 14day flash glucose monitoring system – p160030/s017**

**Sources of the image:** Freestyle Libre 14 Day Flash Glucose Monitoring System - P160030/S017 [Internet]. U.S. Food and Drug Administration.

**D. EVERSENSE CONTINUOUS GLUCOSE MONITORING SYSTEM – P160048/S006**

**Product Name**: Eversense Continuous Glucose Monitoring System

**PMA Applicant**: Senseonics, Inc. 20451 Seneca Meadows Parkway, Germantown, MD 20876

**Approval Date**: June 6, 2019

It is a prescription device that provides real-time glucose monitoring every five minutes for up to 90 days for people with diabetes. The system must be calibrated at least two times per day by testing a fingertip blood sample with a blood glucose meter. This system measures glucose levels in adults aged 18years and older with diabetes for up to 90 days.

**Cautions:**

- The use of Lithotripsy (which breaks kidney stones or gallstones) is not recommended for people who have an inserted sensor because the effects are unknown.
- Diathermy (the generation of heat using electrical pulses) should not be used on people with an inserted

sensor, because energy from diathermy therapy can transfer through the sensor and cause tissue damage in the insertion area.

- Electrocautery which damages the device.


**Fig.6. Eversense continuous glucose monitoring system – p160048/s006**

**Sources of the image:** Eversense Continuous Glucose Monitoring System - P160048/S006 [Internet]. U.S. Food and Drug Administration.

## 6. CONCLUSION:

The treatment of diabetes is an ever-changing field that is progressing to "individualised medicine" with a variety of treatment options currently available. More and more people are being diagnosed with diabetes, and long-term costs continue to be on the rise. In the United States, the total costs of diagnosed diabetes rose to $245 billion in 2012 in comparison to $174 billion in 2007, which represents a 41% increase over 5 years. One of the most prominent components of this medical cost is prescription medications to treat the complications that arise from diabetes. CGM devices have and will continue to make an impact on patients' lives. Companies such as Abbott Laboratories, Medtronic, Tandem, and Senseonics are finding ways to provide the most optimal care for patients with diabetes with a patient-centred approach. With new CGM technologies on the rise, the field of diabetes care looks promising, and continuous glucose monitoring systems serve as a viable option as they increase in popularity and comfort vs the standard home blood glucose device. CGMs are essential tools for monitoring diabetes. In addition to becoming increasingly more accurate and easy to use, CGMs offer helpful features not available with self-monitoring of blood glucose (SMBG) alone, such as glucose trend information, rate of change information, and alerts for unwanted glycemic events. The sensor-augmented pump and new sensor integrated pump products are expanding the usefulness of this tool. CGM has evolved to become a standard part of diabetes management for a wide range of patient populations.

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