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A Review on Continuous Glucose Monitoring System: A Competent Technique in Monitoring and Management of Blood Glucose Levels

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ABSTRACT

Continuous glucose monitoring system (CGMS) is an emerging and widely accepted technique for monitoring and management of blood glucose levels. Blood glucose level can be compared with a tennis ball, the way a tennis ball bounces blood sugar also behaves the same going from high to low rapidly. 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. Continuous glucose monitoring system measures blood glucose level every 5-15 minutes of intervals which helps in having a clear idea of blood glucose level and accordingly dose of insulin that can be administered. This review discusses the history of blood glucose monitoring in the past 100 years, and also gives detailed information on the continuous glucose monitoring system, its working, technology, its wide usage and its superiority over other glucose monitoring techniques and limitations that are to be addressed, and also giving a view on how the future will be of glucose monitoring based on the survey of the variety of literature available on the topic. This review will help readers to understand the continuous glucose monitoring system in the most precise manner and will help to adopt continuous glucose monitoring systems more efficiently in the management of diabetes.

KEYWORDS: *Continuous glucose monitoring system, CGM, History of Glucose monitoring, Future of Glucose monitoring, Flash glucose monitoring, SMBG, Diabetes, CGM sensor technology, Artificial Pancreas, Closed loop system, Glucose monitoring, Glucose monitors*

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INTRODUCTION

Diabetes is one of the largest global health emergencies of this century, ranking among the 10 leading causes of mortality together with cardiovascular disease (CVD), respiratory disease, and cancer. According to the World Health Organization (WHO), non-communicable diseases (NCDs) accounted for 74% of deaths globally in 2019, of which, diabetes resulted in 1.6 million deaths, thus becoming the ninth leading cause of death globally. By the year 2035, nearly 592 million people are predicted to die of diabetes [1]. India has an estimated 77 million people (1 in 11 Indians) formally diagnosed with diabetes, India ranks second most affected in the world, after China. Furthermore, 700,000 Indians died of diabetes, hyperglycemia, kidney disease, or other complications of diabetes in 2020. One in six people (17%) in the world with diabetes is from India [2]. In 2020, according to the International Diabetes Federation (IDF), 463 million people have diabetes in the world of which 77 million belong to India. According to the IDF estimates, India has the second highest number of children with type 1 diabetes after the United States. As Per the World Health Organization, 2% of all deaths in India are due to diabetes [2]. As it all makes the issue of Diabetes very severe and precautionary steps should be taken to control the number of individuals with diabetes.

Type 1 diabetes is a demanding lifelong condition. It requires individuals to measure blood glucose multiple times a day, facilitating insulin dose adjustment in the unrelenting endeavour to achieve normoglycaemia and minimize the future risk of micro and macrovascular complications [3]. Diabetes is characterized by chronic hyperglycemia and causes long-term complications like retinopathy, neuropathy, and nephropathy. It generally accelerates macro- and microvascular changes. Because of lifestyle changes (i.e., eating more and exercising less), diabetes has become a global epidemic [4]. Despite major progress in the care of people living with Type 1 diabetes, many fail to achieve modern glycaemic targets. Blood glucose level can be compared with a tennis ball, the way a tennis ball bounces blood sugar also behaves the same going from high to low rapidly. A key barrier to achieving near-normal glucose levels is the need for frequent finger stick blood glucose monitoring. Pain and inconvenience are recognized reasons for nonadherence with self-monitoring of blood glucose [3].

A continuous glucose monitor is a wearable body sensor that automatically and repeatedly measures glucose at regular intervals (ranging from every 5 to 15 minutes) from interstitial fluid (ISF). Patients or their health care professionals utilize the glycaemic patterns visualized by a CGM to make a lifestyle or medication changes to best improve their blood sugar control. CGM was developed to improve diabetes outcomes, especially A1C and hypoglycemia. Numerous RCTs have demonstrated benefits from using CGM, including either a lower A1C without increasing hypoglycemia, reduced hypoglycemia without improvement in A1C, or both favourable outcomes [5]. This review gives detailed information about the continuous glucose monitoring system (CGMS), its sensor, the technology involved, its Advantages, Disadvantages, History, and future of CGMS technology.

History of Blood Glucose Monitoring:-

Diabetes is characterized by chronic hyperglycemia and causes long-term complications like retinopathy, neuropathy, and nephropathy. It generally accelerates macro- and microvascular changes. Because of lifestyle changes (i.e., eating more and exercising less), diabetes has become a global epidemic [4]. 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 [6]. Various inventions were made from time to time to measure blood glucose levels. The important breakthrough are listed below to give a brief idea explaining how the blood sugar levels were checked in earlier times and how the new methods were developed to check BSL from time to time.

- By 1925, home testing for sugar in the urine was introduced which involved the process of eight drops of the patient's urine being mixed in a test tube with 6 cc of Benedict's solution, all components of which were dispensed by a physician at the time. The instructions required that the test tube be placed in boiling water for several minutes and depending on the colour change observed, the patient would know their sugar level Green represented light sugar in the urine, yellow represented moderate sugar, and red/orange presented heavy sugar [6].
- By the late 1940s, Helen Free developed the "dip-and-read" urine test known as Clinistix, which was capable of monitoring urine glucose levels virtually instantaneously [6].Free's team was able to embed the reagents on a filter paper strip comprising the first test specific for glucose, with release in 1956. This advancement used a double sequential enzymatic reaction via glucose oxidase, peroxidase, and orthotolidine. In this reaction, glucose oxidase catalyzed 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 ortho-toluidine into a deep blue chromogen which was the visual indicator of glucose level [6].
- The first test strips for blood glucose were developed in 1964 by Earnest C Adams and were known as Dextrostix from Ames-Miles Laboratories. It was the first ever dry-reagent blood sugar test strip. It used the same glucose oxidase/peroxidase reaction as the Clinistix but with an addition of an outer semipermeable membrane. This semipermeable membrane was capable of trapping red blood cells but allowed glucose to pass through the membrane to react with the aforementioned dry reagents. The stepwise approach for this test, developed by Anton Clemens from Ames-Miles, required a drop of blood to be placed on the paper strip for 1 min, and then to be washed off. The colour that remained was compared to a standard colour chart, providing a rough estimation of a patient's blood glucose levels. However, there were limitations. This test required a large drop of blood (30uL), and a reaction time of 60 s, and it was reliant on colour matching. Dextrostix laid the foundation for the future area of research known today as blood glucose meters [6].
- The first portable glucose meter, Ames Reflectance Metering, was created in the late 1960s and became available in 1970. Since then, self-monitoring of blood glucose (SMBG) has become possible. Self-monitoring blood glucose meters are portable devices that measure blood glucose concentration on a drop of capillary blood

using finger-stick blood samples and test strips. Since the meters and reagent strips costs have been reduced, SMBG has become the most widely used method for measuring blood glucose levels. Nowadays, SMBG is an essential tool in diabetes self-managing. By enabling patients to monitor their blood glucose levels, significantly improved glycaemic control and diabetes management among diabetics have been observed. However, pain associated with the finger prick is one of the biggest limitations of this method. Another weakness of this method is the insufficient sampling frequency. The SMBG provides only the current capillary blood glucose concentration without information about the glucose trend. Intermittent capillary glucose testing with three to four finger-stick tests provides a snapshot of day-to-day glucose control [7].

- As early as 1962, Huisman and Dozy had shown the increase of the HbA1 fraction in red blood cells of diabetic patients, raising the hypothesis of a reaction of HbAo with “components other than glutathione”, but not especially with glucose. The interest in HbA1c increased rapidly when Rahbar described in 1968 the elevated percentage of this fraction to total hemoglobin in diabetic patients. One of the first systematic demonstrations of HbA1c increase in diabetic patients was made by Trivelli et al. in 1971[8].

Continuous Glucose Monitoring System (CGMS):
A continuous glucose monitor is a wearable body ensor that automatically and repeatedly measures glucose at regular intervals (ranging from every 5 to 15 minutes) from interstitial fluid (ISF). Patients or their health care professionals utilize the glycaemic patterns visualized by a CGM to make a lifestyle or medication changes to best improve their blood sugar control [5].

In 1999, a new era in diabetes care began as the first-ever continuous glucose monitoring (CGM) system was approved to help people diagnosed with diabetes. 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 (IF) over the course of the entire day. For patients with Type I diabetes, it is recommended to have 4 blood glucose readings per day. With CGMs, instead of the 4 readings per day, patients and medical providers now have detailed knowledge of the fluctuations each unique patient experiences throughout the course of 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. An additional benefit of CGM is the detection of hypo and hyper-glycemia. The most up-to-date 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 greater risk of stroke, vision loss, kidney disease, amputations, and even death [6].

Continuous glucose monitoring actually provides utility in a wide range of patients with type 1 DM, including:
1. patients regularly and frequently performing SMBG
2. those who have frequent hypoglycemia episodes with hypoglycemia unawareness
3. those with clinically significant glycaemic variability
4. those with A1c levels above goal
5. those whose SMBG values do not match their corresponding A1C values
6. those who are participating in sports or high-risk occupations and need to avoid hypoglycemia
7. Other patient groups such as insulin treated patients with type 2 DM, noninsulin treated patients with type 2 DM, and pregnant women may also benefit from CGM, however additional evidence from randomized controlled trials (RCTs) of CGM are needed in these populations [9].

Components of Continuous glucose monitoring system:-
There are generally three parts of Continuous Glucose Monitor that are
1. Sensor
2. Transmitter
3. Receiver

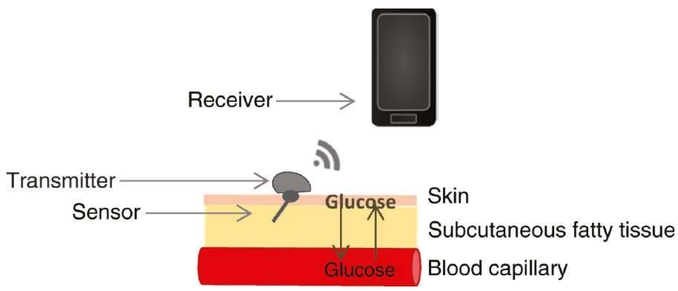

Fig 1:- Components of CGMS

1. Sensor:-
The sensor is easily inserted just under the skin with an applicator and is used to measure glucose levels. Sensors are typically placed on the abdomen but some sensors are approved for use on alternate body locations. The sensor has a small adhesive to hold it in place [10].

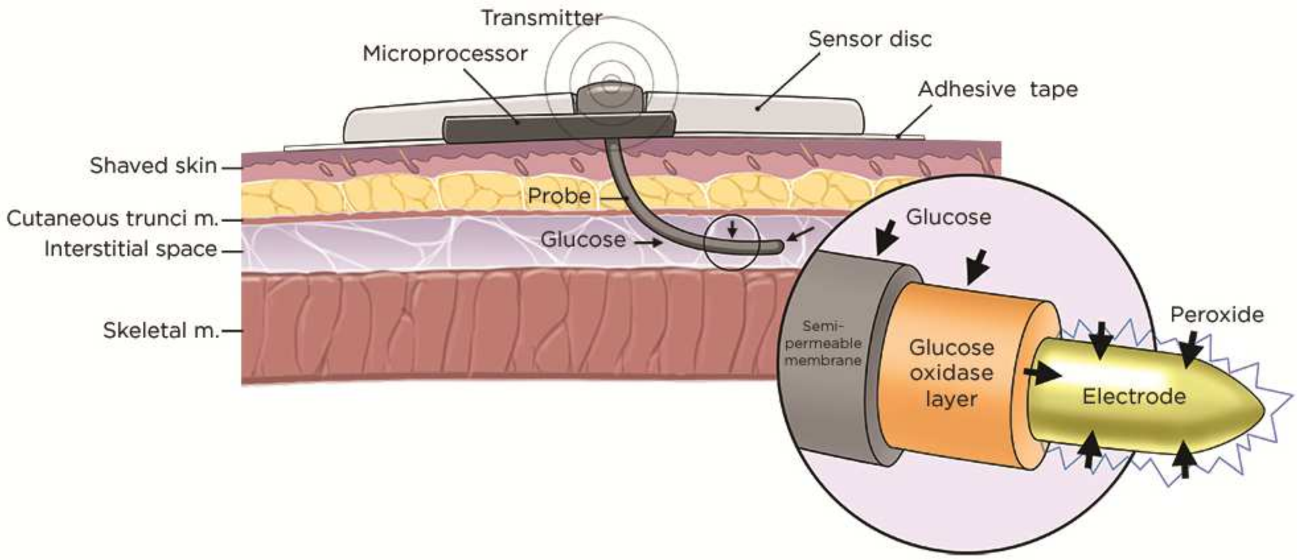

Fig 2:- Senser Used in CGMS Devices

2. Transmitter:-

The transmitter is a small, lightweight piece that fits onto the sensor. The transmitter wirelessly sends the glucose data from the sensor to the monitor or an insulin pump if the sensor is integrated with a pump [10].

3. Receiver:-

The receiver is a slim, portable and discreet component that is carried by the user and displays the glucose information sent from the transmitter. This device displays the current glucose level as well as the trended information. The receiver also alerts the user in the case of impending highs and lows [10].

Fig 3:- Transmitter and Receiver

Alarms:-

Many CGMs contain alarms that automatically notify the user when certain glycaemic patterns are detected. Threshold alarms sound after the glucose concentration is either below or above a predefined range and warn a patient to take corrective action. Rate-of-change alarms sound when the glucose rises or falls above a certain velocity. Predictive alarms sound when a proprietary algorithm, based on the absolute glucose concentration and the rate of change of the glucose concentration, predicts a glucose concentration outside of a predefined range. Predictive alarms allow patients to take preventative rather than only corrective action [5].

Data obtained from CGMS:-

Data obtained from CGMS is in Graphical form as well as individual readings also can be obtained. The graph shows the trends occurring in Blood glucose levels throughout the day. The target range is already set so by the reference from the graph one can judge whether the sugar levels are in range or whether frequent hypoglycemia or hyperglycemia events are occurring. By referring to the graph obtained from CGMS the registered medicinal practitioner can give the best possible treatment to the patient where the ultimate goal will be of maintaining the sugar level in a target range. The alarms for high and low sugar are also incorporated in CGMS which gives alerts about the high and low sugar that the patient is unaware therapeutically and the situation can be treated before it reaches a greater level of severity.

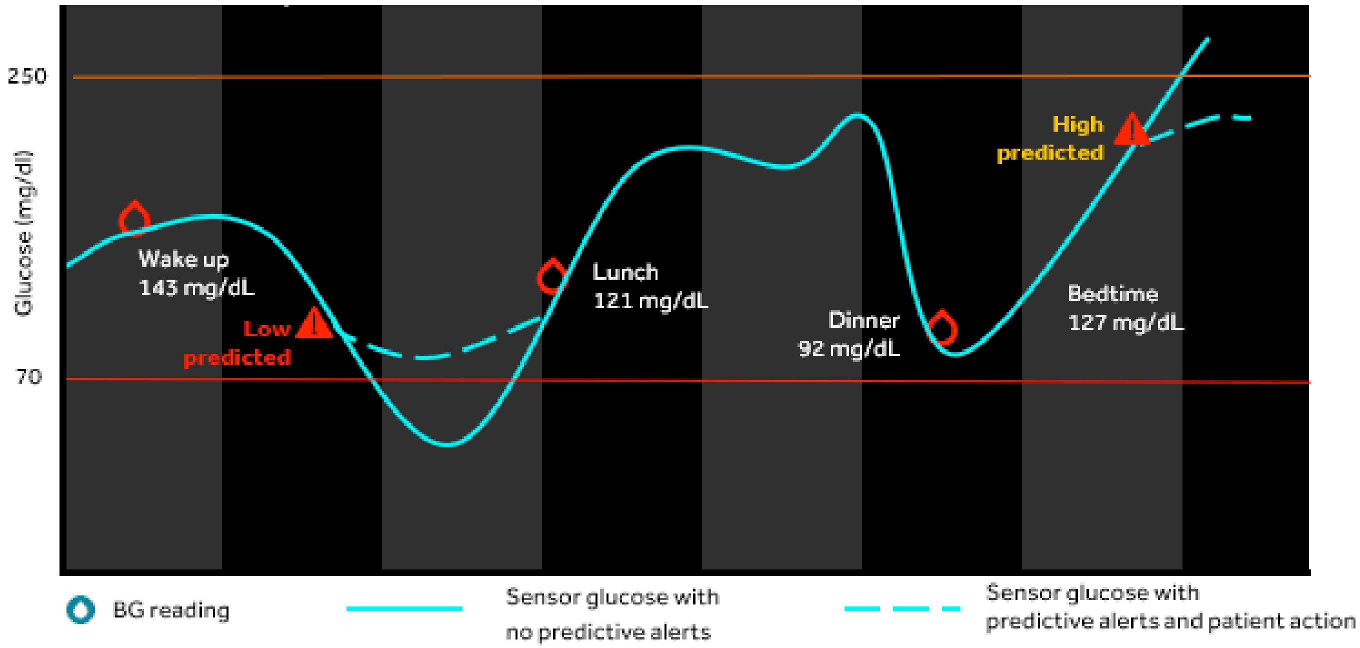

Fig 4:- CGMS Graph

CGMS vs SMBG (Finger stick method):-

1. The traditional method of measuring blood glucose levels is a finger stick blood glucose measurement that is displayed using a blood glucose meter (BGM). The BGM provides a single glucose reading at a single point in time [10].
2. The key difference between CGM and BGM is that CGM provides continuous glucose readings throughout the day and night. Beyond just the glucose readings, CGM displays a glucose trend graph and direction arrows that allow people with diabetes to anticipate approaching glucose highs and lows [10].
3. Compared to self-monitoring of blood glucose (SMBG) with a traditional glucose meter, CGM measures glucose automatically and as often as every five minutes, which generates 288 measurements per day. SMBG requires patient initiation and rarely generates more than 4-7 measurements per day.
4. For CGM, measuring glucose hundreds of times each day requires no additional pain, blood waste, or financial cost beyond the baseline costs of using CGM.
5. Beyond simply increasing the quantity of glucose measurements, CGM also provides trend information about the direction and rate of changing glucose concentrations.
6. Most real-time CGM products can sound alerts to warn of low, high, falling, or rising glucose levels, whereas SMBG does not. Such alerts are uniquely able to inform patients of important glycemic events when they are otherwise not aware, such as during sleep or when the patient is occupied with other activities.
7. Finally, if a CGM can be integrated with an insulin pump, then the CGM can automatically adjust or suspend basal insulin delivery in response to glycemic trends.
8. A disadvantage of CGM compared to SMBG is that CGM sensors will occasionally fail or generate outlier data points that can be further off than most outlier data points of SMBG.
9. Therefore, non-adjunctive use, meaning that treatment decisions should not be based on CGM data alone. Instead, patients were required to verify the CGM information with a confirmatory finger stick glucose measurement.
10. This changed in December 2016, when the FDA approved the Dexcom G5 Mobile CGM system (Dexcom, San Diego, CA) as the first CGM where treatment decisions could be made without a confirmatory finger stick test [9].

Features	CGMS	SMBG
Provides Continuous Glucose Data	Yes	No
Show the rate and direction of glucose change	Yes	No
Research shows the use has improved time in target range and reduced A1c, hospital admission, hypoglycemia	Yes	No
Personalized alerts to help identify hypo/hyperglycemia	Yes	No
Graph on trends of sugar throughout the day	Yes	No
Patients initiation to check glucose required	No	Yes
Pain and loss of blood occurs	No	Yes

Example explaining CGMS & SMBG data:-

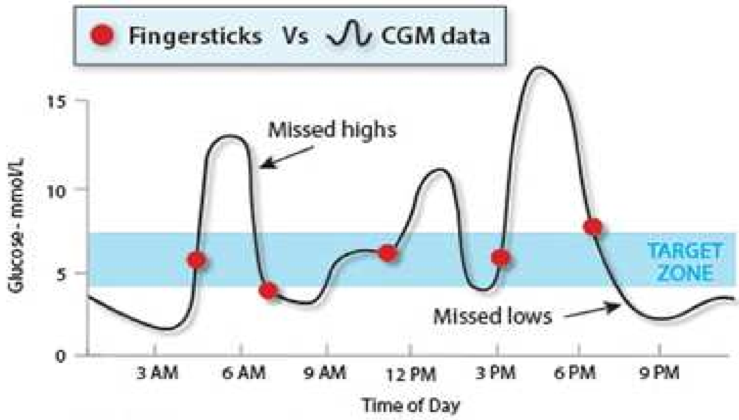

Fig 5:- CGMS VS SMBG Data

In the above example, the graph obtained by CGMS data is compared with the finger stick method which is Self-monitoring of blood glucose (SMBG). It shows that CGMS data shows every high and low sugar occurring throughout the day. But the finger stick method misses the important highs and lows in sugar throughout the day and only shows the sugars that are in the target range. This is because of the limitation of the finger stick method of not being able to measure the data as frequently as CGMS. By the readings of the finger stick method, a Registered medicinal practitioner will consider the excellent management of blood glucose and give the treatment accordingly which can result in serious effects of Diabetes and hospitalization can be required.

Advantages of CGMS:-

1. The main advantage of continuous glucose monitoring is that it can help identify fluctuations and trends that would otherwise go unnoticed with intermittent finger stick measurements [10].
2. There is no question that relative to SMBG, use of CGM can dramatically improve the quality of glycemic control both in type 1 and type 2 diabetes [11].
3. The benefit is especially pronounced in high-risk patients with frequent or severe hypoglycemia, often associated with hypoglycemia unawareness [11].
4. Offers alerts:- The most significant benefit of all real-time CGM systems is having audible alarms that can warn you if your blood sugar (blood glucose) is getting too high. This allows time for adjustments that could lessen the impact of high or low blood sugar or avoid it altogether [6].
5. Shares data:- The ability to share data with family members and friends is another important feature. It acts as a safety net, especially when traveling. For example, if you don't wake up to a low glucose alarm during the night, someone else will be alerted and can get in touch with you [6].
6. Eliminates finger sticks. While not all real-time CGMs offer this benefit, some allow you to make treatment decisions—how much insulin to dose, for instance without the need for finger-stick confirmation. Plus, some are factory calibrated, eliminating the hassle and pain of calibrating with finger sticks [6].
7. Glucose readings at the push of a button. Easy and discreet view of up to 288 glucose readings per day [10].
8. Trend arrows that reflect the speed and direction of glucose level to help avoid impending lows and highs with appropriate action [10].
9. Trend graphs to offer a retrospective view of the effect on glucose levels from things like food, exercise, medication and illness [10].

10. Reduction in Haemoglobin A1c without increasing low blood glucose events [10].
11. Short-term masked CGM can be used to detect problems, evaluate quality of glycemic control, describe patterns of glucose, assess risks of hypoglycemia and hyperglycemia by time of day and day of the week. This can be helpful to the physician and patient [11].

Disadvantages:-

1. LAG Time:- Time taken by glucose to equilibrate between blood and interstitial fluid compartments is called lag time. CGMs measure glucose in interstitial fluid, which can lag 5-15 minutes behind the blood glucose, especially when the blood glucose levels are changing rapidly. the difference in reading between blood and interstitial fluid can be about 10-20% or greater [9].
2. CGMS cannot be used as a replacement for glucose meters because it does not satisfy conventional goal performance criteria for in vitro glucose measurements and can lead to clinically incorrect treatment decisions [12].
3. most of the devices need to be calibrated 2- 4 times a day during the time when the blood glucose is most stable [13].
4. CGMs are expensive and require sensor changes every 3-14 days depending on the type of sensor [13].
5. There can be false alarms due to physical compression of the sensor, which can be inconvenient for the patient [13].
6. Certain medications can interfere in the accuracy of the sensors, as listed in. Most common is the use of acetaminophen, which can lead to false elevation in the sensor glucose levels due to interference in the mechanism of action of the sensor. e.g., Acetaminophen, Bilirubin, Cholesterol, Creatinine, Dopamine, Ephedrine, Methyl dopa, Ibuprofen, Tetracycline, Tolbutamide, Triglycerides, Vitamin C, etc [13].
7. More research is required in order to use CGM during pregnancy, in dialysis and in critically ill patients. Use of noninvasive epidermal glucose sensors seems promising [13].
8. Sensor lifetime:-Sensor lifetime is another factor that contributes to cost, inconvenience, and slow user acceptance. Even the durability of the adhesive used for attachment of the sensor to the skin is a matter of concern. One can expect that user acceptance will continue to improve as sensor lifetime increases and ease of sensor insertion improves [14].
9. Calibration:- Calibration using capillary blood glucose meters and reagent strips involves cost, discomfort, and inconvenience, increases the number of devices and complexity, and may add psychological burden [14].
10. Devices can be expensive in comparison with Glucose meters.

➢ **Comparison Between different Brands of CGMS:-**

CGMS Brand	Dexcom G5	Dexcom G6	Medtronic Guardian	Freestyle Libre Flash	Eversense
Calibration Required?	Yes	No	Yes	No	Yes
Frequency of calibration	12 hours	None	12 hours	None	10-14 hours
Can administer insulin referring to senser readings	Yes	Yes	No	Yes	Yes
Frequency of sensor to be changed	Every 7 days	Every 10 days	Every 7 days	Every 14 days	Every 90 days
Warm up period	2 hours	2 hours	2 hours	1 hour	24 hours
Easy to insert?	No	Yes	No	Yes	Requires medical procedure
Alarms and alerts?	Yes	Yes	Yes	No	Yes
Predicts lows and highs	No	Yes	Yes	No	yes
Connects with insulin pumps	No	Yes	Yes	No	No

Recent Advancement and Future of CGMS technology:-

Future sensors under development (compared to current sensors) are intended to:-

1. Require less frequent calibration [9]
2. Last Longer [9]
3. Be smaller and less obtrusive [9]

4. Be more accurate [9]
5. Integrate more closely with pumps to create closed loop systems utilizing additional input from non-glucose sensors [9].

CGMS technology is going to be highly useful for not only just for monitoring glucose but in overall management of diabetes. There is ongoing research in developing devices that monitor interstitial fluid, blood or other body fluid glucose levels noninvasively, such as by using electrochemical sensors worn on the skin. The sensors being developed and currently under trial include small meters strapped to the arm, skin patches, contact lenses and tattoos. More research is needed to assess if perspiration, ocular fluid and saliva can be used to monitor glucose instead of blood or interstitial fluid [13]. The various advancements that are going on in CGMS technology are

1. Flash glucose monitoring:-

The Libre Flash:- The Libre Flash is another CGM type system, which enables continuous interstitial glucose monitoring without the need for blood glucose calibration, as it is factory calibrated, but the continuous data is only available for 8-hours retrospectively on user prompt. The system uses a glucose sensor inserted into the skin over the triceps and a reader is used to scan over the sensor in order to display the last 8-hours of glucose readings, with a reading every 15-minutes. The sensor is factory calibrated and each sensor can be worn for up to 14 days [13].

2. Closed loop system or Artificial pancreas:-

Closed-loop technology or the artificial pancreas is medical device system that has 3 components. The components consist of the CGM, which is connected wirelessly to the insulin therapy delivery function carried out by a pump and a digital controller. The digital controller analyzes the data and makes decisions about any insulin therapy adjustments needed and instructs the pump accordingly. Integrating these 3 functions together creates an automated closed-loop system. The first hybrid closed loop system in the United States was introduced by Medtronic in 2017 and was called the Medtronic 670 G with automatic basal rate adjustments without bolus automation. Development of fully automated closed loop systems utilizing both insulin and glucagon are underway.

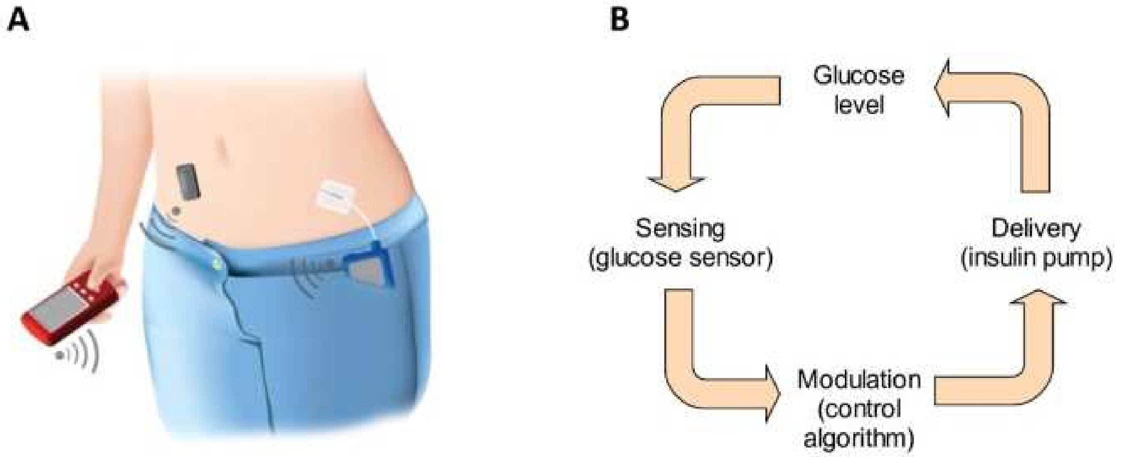

Fig 6:- Closed loop system or Artificial pancreas

3. Optical methods:- Optical glucose sensing is the most widely studied method, for the development of non-invasive blood glucose measurement. Even though none of the optical based biosensors that meet clinical accuracy are commercialized yet, several researches are undergoing [15].
4. Electromagnetic method:- Electromagnetic sensing involves measurement of bloods dielectric properties detected through changes in eddy currents using electromagnetic coupling between two inductors. The change in blood glucose concentration results in the variation of bloods dielectric properties such as permittivity and conductivity. This causes changes in the electromagnetic coupling of nearby inductors affecting their impedances which results in variations in resonant frequency. The variations in frequency shift helps to determine bloods dielectric properties correlated with the concentration of glucose [15].

Conclusion:-

CGMS was developed with the intention of improving diabetes outcomes, especially A1C and hypoglycemia but if used correctly CGMS can be used in various prospectives by which patients can be treated more effectively and good results can be obtained with minimum side effects. The implementation of CGM has improved HbA1c levels and also reduced the incidence of hypoglycemic events [13]. One study shows that CGM is a well-tolerated and versatile tool for obesity research in both pediatric and adult patients [16]. Another study concluded that CGMS could be useful in routine clinical practice to provide much more information on the glucose profile than intermittent self-monitoring of blood glucose (SMBG) [12]. CGMS sensors when incorporated with insulin pumps can result in better management of diabetes which is commercially known as an artificial pancreas or closed-loop system [17]. Research is underway to assess whether glucose levels can be monitored in other body fluids such as perspiration, breath, ocular fluid, and saliva [13]. LAG being the limiting factor in the whole CGMS technology more research should be done to minimize the side effects occurring due to lag. More research should be carried out on pregnant ladies so that management of gestational diabetes will become more sophisticated. Considering overall scenarios CGMS technology if used properly can be helpful in increasing the quality of lifestyle in diabetic as well as non-diabetic people and can cause a positive impact on the healthcare system.

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