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A REVIEW ON: MEDICAL DEVICES USED IN DIABETES

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ABSTRACT
The management of diabetes is progressing rapidly from the use of traditional finger sticks for glucose monitoring and multiple daily injections of insulin to more user-friendly devices and approaches. These advances promise to free people with diabetes from the need for continued daily compliance, thereby improving their quality of life and improving control of their underlying diabetes. An underlying theme to solutions based on percutaneous or fully implanted devices is that the useful lifetime of such devices is often limited by the body's foreign body response. This review briefly outlines general factors associated with point-in-time needle stick approaches to the growing use of short-term percutaneous implants (≤7 days) to the challenges of more extended devices, both technical and regulatory, faced by developers of these devices.

KEYWORDS:

INTRODUCTION

A medical device is any instrument, apparatus, in vitro reagent, implant, or another similar or related item that is intended to be used in the diagnosis of a disease or other condition, in the cure, mitigation, treatment, or prevention of disease, or that is intended to affect the structure or any function of the body, but which does not accomplish any of its primary intended purposes through its chemical action on or within the body.

In India medical devices are governed by CDSCO (Central Drugs Standard Control Organization) which is regulated by the Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India. CDSCO is the only government body that regulates medical devices.

Many committees, like the Mahelkar Committee – Central Drug Standard Control Organization, had been set up and given their opinion and recommendation. All these are now being taken into to form the Indian Medical Device Regulatory Act (IMRDA).

What is DM?

A condition in which the body is unable to regulate the quantity of glucose (a form of sugar) in the blood and the kidneys produce an excessive volume of urine. This illness develops when the body does not produce enough insulin or does not use it properly.

Diabetes mellitus is an increasingly prevalent disease in the USA that is associated with significant morbidity and mortality. In 2015, 30.3 million Americans had diabetes, comprising 9.4% of the US population. Diabetes is associated with significant distress and financial burden on individuals living with the disease and on society as a whole. In 2017, diabetes medications and supplies accounted for 15% of the estimated US$237 billion in direct medical costs for diagnosed diabetes. In 2023 37.3 million people have diabetes (11.3% of the US population) diagnosed 28.7 million people, including 28.5 million adults Undiagnosed**:** 8.5 million people (23.0% of adults are undiagnosed).

Types of DM

1. Type1 DM

In T1DM, beta cells in the pancreas are frequently destroyed as a result of an autoimmune process. Beta cells are destroyed as a result, and as a result, there is no or very little insulin in the body.

2. Type2 DM

The development of T2DM is more gently manifested, with an insulin functional deficit brought on by an imbalance between insulin levels and insulin sensitivity. Although insulin resistance has many causes, fat and aging are the most frequent ones.[1]

3. Gestational DM (Diabetes in Pregnancy)

In essence, gestational diabetes is diabetes that appears during pregnancy. Although the cause of its development is yet unknown, some theorize that HLA antigens, notably HLA DR2, 3, and 4, may be involved. Additionally, it's assumed that high levels of proinsulin

contribute to gestational diabetes, and some research suggests that proinsulin may cause beta-cell stress. Others think that the activity of beta cells and peripheral insulin sensitivity may be impacted by high levels of hormones such as progesterone, cortisol, prolactin, human placental lactogen, and estrogen.[2]

4. Secondary DM

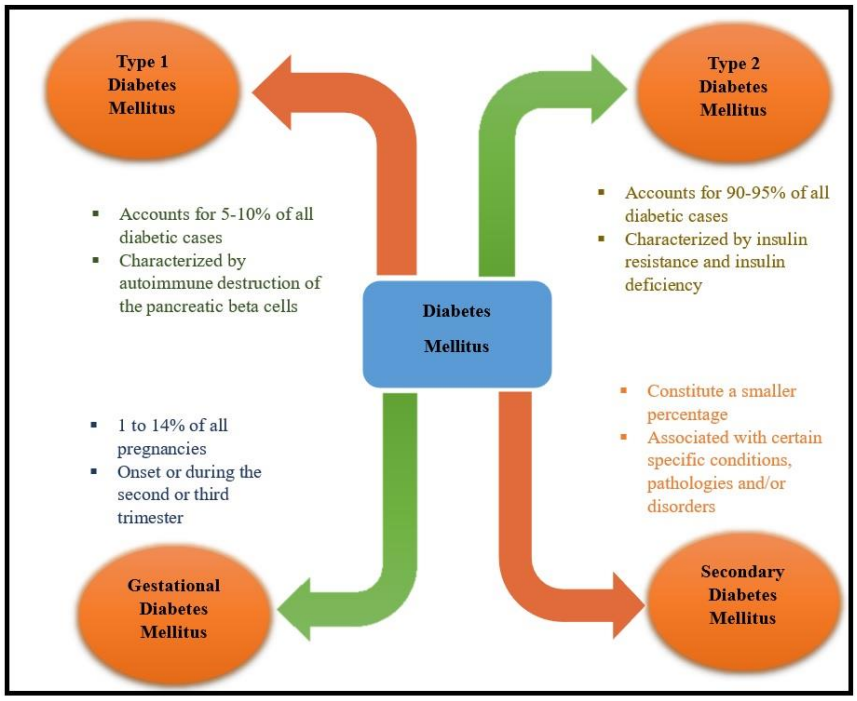

Fig 1: Types of DM.

- **Risk factors of Diabetes Mellitus**

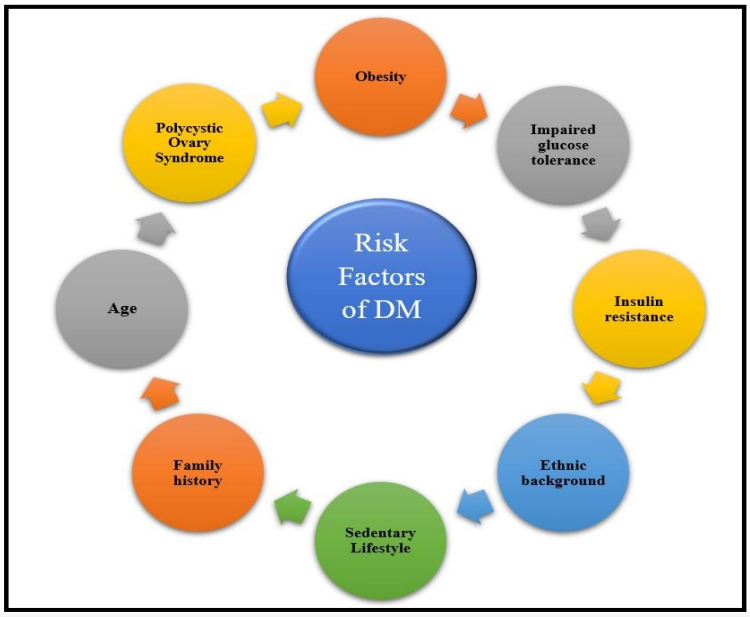

Fig 2: Risk factors of DM.

❖ Pathophysiology of DM, a group of metabolic disorders characterized by hyperglycemia due to the inadequate secretion of insulin (Type1 DM) or reduced insensitivity of cells/organs to insulin (Type2 DM/ Gestational Diabetes).[3,4]

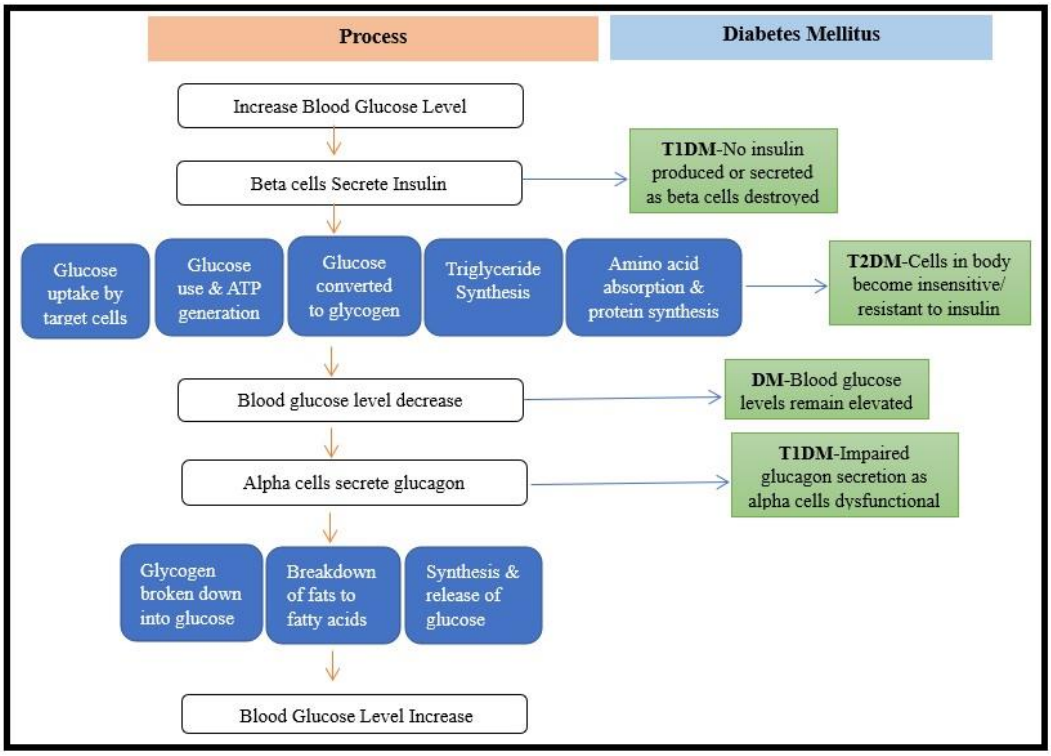

Fig 3: Mechanism of DM.

❖ Types of diabetes devices are currently available:

1. Glucose Monitoring Devices:

A glucometer and a continuous glucose monitor (CGM) are the two tools you can use to check your blood sugar levels. Both tools, when applied correctly, can decrease the possibility of complications from diabetes.

A glucometer is a portable instrument that measures the current level of your blood glucose. A self-applied sensor on a wearable device known as a CGM measures blood sugar levels. It gauges the body's tissue glucose levels.[5]

2. Insulin Pens

An alternative to utilizing an insulin syringe and vial is to use an insulin pen. They are a practical and simple method for administering insulin.

To assist provide a constant amount of insulin with each dose, various types of insulin pens are available. Some connected insulin pens (also known as "connected smart insulin pens") feature sensors that link them to a mobile app. This can record the time and amount of insulin you've injected.

3. Insulin Pumps

A wearable insulin delivery system is called an insulin pump. It releases tiny doses of insulin throughout the day once it has been configured to fit your needs. However, there are times when you'll need to instruct the pump to administer insulin. You might need to do this after eating or if your blood glucose level is abnormal.

Insulin pumps are used by some persons with Type 2 diabetes, while Type 1 diabetics use them more frequently.[6]

❖ **What are the most popular diabetic monitoring gadgets right now[7]?**

The American Diabetes Association (ADA) evaluates goods and equipment to help people with diabetes live their best lives. This also applies to diabetes devices, and one isn't always preferable to another. Your medical needs, level of comfort, and personal preferences will determine which device(s) is/are best. To learn more about glucometers, CGMs, and other devices, consult the ADA Consumer Guide.

Devices for automated insulin delivery (AID) are quite new on the market. With the help of an insulin pump and a CGM, they monitor variations in blood sugar and alter the amount of insulin being administered. This helps prevent very high or low blood glucose levels. Although AIDs has decreased the psychological toll of diabetes, researchers are currently working to improve them.

❖ **What diabetes devices might soon be authorized or approved?**

1) Automated Insulin Delivery (AID) System Evaluation

Although AID technology has advanced significantly since its inception, it still depends on the user (human) to carry out activities. They are also referred to as "hybrid closed loop" devices for this reason. Ideally, these devices would be able to function independently and without your help.

Researchers are working to provide a "hands-off" functionality for AID devices that have received FDA authorization or approval. These devices are also referred to as "closed loop" ones. Once available, they'll probably aid in reducing user error and enhancing overall glucose management when combined with faster-acting insulins.

2) Better CGM devices

Nowadays, CGM devices are worn on the legs, buttocks, stomach, or arms. Depending on the device, they can last for a week or more. What if, though, a sensor didn't need to be inserted with a needle or had a longer lifespan?

A few companies are creating needleless CGM devices that can be clipped onto the ear or worn on the eye. Additionally, a smartwatch is in development. Although these devices are still in their infancy, efforts are being made to produce CGMs that are easier to wear and last longer in the future. It's unclear how long these products will be available.

3) Smart Insulin Pens

There are now smart insulin pen-attachable gadgets such as Bigfoot Unity and InsulCheck on the market. Your insulin pen is linked to an app that monitors your insulin intake. However, connecting these gadgets to your insulin pen can be a problem.

The creation of insulin pens with "smart" parts is underway. They want to make it simpler and more practical to track insulin. Some of these intelligent insulin pens are already on the market, but only for specific kinds of insulin. In the next two to three years, more of these devices could hit the market.

4) Oral Insulin

The development of oral insulin has been a focus of research. Even if these attempts have so far proven ineffective, research is still being done.

Patients are now being enrolled in phase 3 clinical study by one business, OraMed, to determine the efficacy of their oral insulin medication.

5) Insulin Patches

The development of intelligent insulin patches is still in its early phases. These skin patches that you can wear are designed to administer insulin to your body gently.

There are already a few insulin patches on the market. The current generation of insulin patches resembles an insulin pump in appearance, although they operate somewhat differently. Without the need for injections, they provide fast-acting insulin during meals and lower high blood glucose levels. They may operate in a manner that is comparable to that of products like nicotine patches.

6) Foot Ulcer Sensors

Diabetes increases the risk of nerve and blood vessel issues, which can harm the health of the feet. Changes in glucose levels during the day may be a factor in problems with circulation, numbness, and pain. This may result in infections, foot sores, and poor healing. One example is the design of sophisticated shoe insoles.

7) Digital therapeutics for diabetes management

Smartphone apps that assist in managing health issues are a form of digital therapy.

These apps can monitor prescriptions, and glucose levels, and assist with daily decision-making when it comes to diabetes. Some AID systems even permit the programming and administration of insulin using an app. This is a practical choice, for instance, if an insulin pump is hidden by a garment or several layers of clothing.

In the future, in addition to your meds and supplies, your doctor might also recommend a diabetes app. Diabetes is on pace to follow in the footsteps of other health disorders like ADHD, which currently have treatment options that employ this method.[7]

Table 1: Devices available for DM.

Class of device	Device	Manufacturer	CE mark approval date
Implantable CGM devices	Implantable Eversense CGM sensor	Senseonics Inc.	2016
Implantable insulin pumps	MiniMed MIP2007C	Medtronic	2013
	Diaport	Roche	2012
Automated insulin delivery devices			
Hybrid closed-loop systems	MiniMed 670G	Medtronic	2018
	MiniMed 780G	Medtronic	2020
	Control-IQ	Tandem diabetes care	2020
	DBLG1	Diabeloop	2018
	Inreda AP	Inrede diabetic	2016
	Tidepool loop	Tidepool	Pending
	Omnipod 5 system	Insulet	2022
	iLet Bionic Pancreas	Medtech Beta Bionics	Pending

	System		
	CamAPS FX	CamDiab	2020
Fully closed-loop systems	CamAPS HX	CamDiab	2020*

❖ **Overview of the design and analysis of clinical trials using high-risk medical devices for the diagnosis and treatment of diabetes instruments for monitoring diabetes in those at high risk[8]**

Nine significant clinical studies were included in eight PMAs for CGM devices; P160048 reported two of these, the PRECISION and PRECISE II investigations. All nine of these non-randomized, single-arm, prospective, multicenter studies were included. Six crucial clinical studies enrolled individuals at 3 to 8 centers, whereas the other three studies did not specify the number of centers. These 9 critical clinical studies included mean (SD), median (minimum, maximum), and 71.9 (20.5), 72 (35, 91) patients, respectively. Patients with type I or type II diabetes participated in eight investigations, including the crucial clinical trial of P050020[9]; The only type I DM patients were included in the Navigator Continuous Glucose Monitoring System. In 7 of the 8 studies, the percentage of type I DM patients was mentioned, with a mean (SD), median (minimum, maximum), and 80% (67.8%, 95.8%) as the minimum and maximum values, respectively. The majority of important clinical studies include both in-clinic and home usage components, with the in-clinic component receiving the most attention during analysis. The individuals in various crucial clinical studies wore the electrochemical sensors of the glucose monitoring system for anywhere between a 5-day study and a 1-week follow-up visit (P050020[10]; a 12-hour warm-up period (P160030, FreeStyle Navigator Continuous Glucose Monitoring System) to 10 days.[11] Alameda, California-based FreeStyle Libre Flash Glucose Monitoring System) or up to 90 days of use (P160048[12], Glucose monitoring system by Eversense). The length of the study was determined by the total reported use life after sensor application for each item. Frequent sample testing (FST) was used for in-clinic testing. Blood samples were taken every 5 to 15 minutes, and the FST took place for 4 to 12 hours, usually at the start, middle, and conclusion of the CGM use days. Except for a few patients in P120005, every participant in each of the nine pivotal clinical investigations was fitted with two to three sensors.[13] (Dexcom G4 PLATINUM Continuous Glucose Monitoring System, San Diego, CA) and the critical clinical study P160048 that only received 1 sensor. The first and secondary sensors were specified in just three clinical studies from the P160030 and P160048 submissions, and the analysis of effectiveness was based on all data points gathered from the primary sensors worn by the study subjects, whereas other studies analyzed data from all inserted devices. Qualifying participants in two important clinical studies (P150029,[14] iPro2 Continuous Glucose Monitoring System, and P160048) performed hyperglycemia and hypoglycemia challenges during sensor clinic visits. Evaluation of the system performance to laboratory reference measurements on venous blood samples for all study participants was the main goal of the crucial clinical studies for the CGM. The comparison between data from the suggested glucose monitoring devices and blood glucose readings obtained using a clinical laboratory reference method, often the Yellow Springs Instrument (YSI) during in-clinic visits, served as the foundation for the efficacy measurements.

Medical devices for the treatment of high-risk diabetes. The seven devices used for diabetes treatment are all insulin delivery systems (insulin pumps or APDSs), and they are all often combined with a particular CGM sensor and transmitter to identify trends and tracking patterns in diabetic patients. In addition to evaluating the effectiveness of the paired CGM to laboratory reference readings that are comparable to those mentioned in the section on high-risk diabetes monitoring medical devices, this is another objective of the major pivotal clinical studies for these therapy devices. P130007 For 2 of the 4 insulin pumps[15], Animas Vibe System and P140015.[16] The other artificial pancreas device (P150001) accomplished new pivotal accuracy testing, while MiniMed 670G System.[17] MiniMed 630G System with SmartGuard) referred to the clinical research detailed in the SSED of the previously approved comparable device. Patients with type I or type II DM were enrolled in each of the five clinical accuracy studies (P150001 referred to the same study as P120010, and P180008 lacked a complete performance evaluation study), and the mean (SD), median (minimum, maximum), and total number of participants for these pivotal clinical studies, respectively, were 103.4 (41.3), 90 (72, 176). The total mean (SD), median (minimum, maximum), and a number of sensory-matched pairs were collected in these five pivotal clinical studies for the effectiveness analysis. The mean (SD), median (minimum, maximum), and number of total readings falling within the range of 15 mg/dL or 15% and 20 mg/dL or 20% are all 66.7%. Only people with type I diabetes were included in the 4 clinical investigations, and each study's methodology was unique. To evaluate the effectiveness of the threshold suspend tool, the supplementary clinical investigations of the P120010 and P180008 submissions used randomized, straightforward, two-period, two-treatment cross-over studies. The threshold suspend tool has two treatment options: "ON" and "OFF." These 2 clinical investigations.

Table 2: Indications, limitations & contraindications of continuous subcutaneous insulin infusion therapy in patients with diabetes.

Long-term indications	Short-term indications	Contradictions
Elevated $HbA1_c$ with MDI therapy	1. Acute situations: a) For the treatment of mild ketoacidosis or acute hypoglycemia b) For acute infections c) undergoing enteral alimentation	1. Absolute contraindications: a) Severe psychiatric disorders b) Progressive ischemic or proliferative retinopathy c) Due to the patient's environment or insulin pump: A non-educated medical environment Living with extreme circumstances of either heat or cold for professional & personal reasons Underwater diving Exposure to high electromagnetic fields (NMR)
2. Marked same-day or between -day glucose level fluctuations	2. Transient situations: a) Severe painful neuropathy b) Chronic infections, foot ulcers,& all wound healing cicatrization situations c) Pregnancy or the intention to become pregnant	2. Relative Contraindications: a) Poor compliance or patient reduction to live with the current management of treatment (ex; frequent visits to diabetes center, glycemia monitoring, ketosis testing) b) Poor local hygiene and/ or staphylococcus presence c) In some cases of end-stage renal failure because of acidosis risk attributed to patient incompliance d) Sensory or gestural impairment (difficulty with technical aspects of pump management)
3. Variability of insulin requirements: a) Endogenous causes: dawn phenomenon b) Exogenous causes: work type particularities (ex; shift workers or business travelers)		
4. Recurrent hypoglycemia (severe or non-severe): a) Failure to maintain $HbA1_c$ targets (<7%) without the occurrence of disabling or frequent symptomatic or asymptomatic hypoglycemic events (>4/week) b) Incidence of >1 episode/year of unexplained severe hypoglycemia		
5. Other reasons: a) Allergy to insulin b) Lipoatrophic diabetes c) Very low insulin requirements		

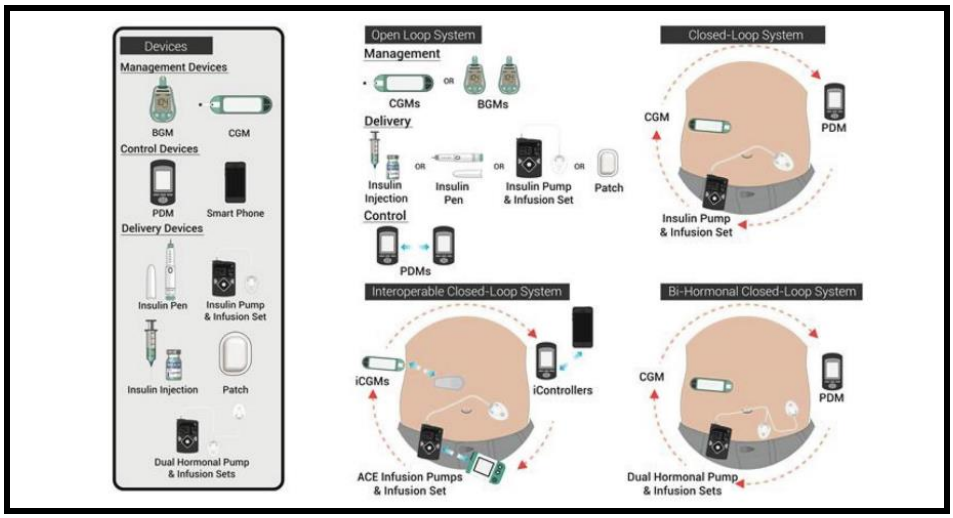

Fig 4: Schematic of the main devices used in DM treatment and their coupling to form open-loop systems (hybrid or fully automated), interoperable closed-loop systems, and bi-hormonal closed-loop systems.[18]

Future perspective

Due to significant advancements in DM therapy, people now have a variety of options for precisely controlling their blood sugar levels. Thanks to improvements in CGMs and insulin delivery systems, there will be more treatment options in the coming years. Although open loop systems continue to be the primary method for controlling T2DM and GDM, a transition to more automated, networked systems should take place soon. For DM patients, especially those with T1DM, hybrid closed-loop systems already provide some automation, personalization, and interoperability. Interoperable automated glycaemic controllers integrated continuous glucose monitors, and alternative controller-enabled infusion pumps have all been created as a result of recent changes in FDA regulations. The review of these devices through the 510(k) process will increase the number of interoperable devices available on the market in the upcoming years. The "interoperability puzzle" will be solved with the arrival of more interoperable controllers that can power compatible integrated continuous glucose monitors and alternative controller-enabled pumps.[19] As they take into account parameters like diabetic condition, age, lifestyle, and finances, the coupling of interoperable components would create more flexible and effective treatment solutions for DM patients. To further reduce the frequency of hypo- and hyperglycaemic episodes and lengthen the time spent in range, fully automated closed-loop and dual hormonal systems are being developed. Because they enable people to regulate their illness and as a result reduce treatment commitment, responsibility, and stress, closed-loop systems have frequently been described as the "Holy Grail" of T1DM treatment.[20] By receiving this classification, businesses are given access to priority communication and review, which helps to hasten the creation and evaluation of their products. CamDiab has made significant strides toward the creation of completely automated systems in Europe, and its most recent software demonstrates ideal glycemic management in T2DM patients receiving dialysis.[21] These technologies are anticipated to pave the way in closing the loop and minimizing the need for decision-making. The much-needed replacement for present insulin injection technology and hybrid closed-loop systems could be smart responsive pharmaceuticals. In response to changes in BGLs, a variety of new biomaterials that have recently been produced demonstrate promising capacities to initiate and regulate drug release. If these technologies can address the current operability difficulties (reloading, dosage, and durability) will be determined by future clinical investigations. To better regulate dose and pharmacokinetics, these responsive technologies will probably be implemented into already approved medications or innovative medical devices.[22] Additionally, technology that may release insulin during hyperglycemia or glucagon during hypoglycemia in response to BGL fluctuations, simulating the actions of a non-diabetic pancreas, could greatly enhance the quality of life for DM patients. The best chance for people with insulin-dependent diabetes to regain endogenous control over BGLs is through islet transplantation. Currently, islet transplantation is permitted for use in patients with brittle T1DM in Canada, Australia, the United Kingdom, and certain other European nations. As a result, national healthcare systems in these countries or insurance companies are responsible for paying the costs of islet transplantation. Donislecel, an allogenic islet transplant medicine for people with brittle T1DM, received FDA approval for its biologics license application 125,734 in April 2021. This is a significant development for islet transplantation.[23,24] Research is currently being done to create encapsulation techniques that will shield transplanted islets from the recipients' abnormal immune response, doing away with the requirement for immunosuppressants[25]; While providing islets with a blood supply (revascularization, growth factor administration), oxygen (refillable oxygen supply, oxygen-producing materials, or direct contact with ambient oxygen), and a blood supply to offer nutrients and enhance cell activity. Future research on encapsulation methodologies will also address the following issues: (i) device lifetime and administration frequency; (ii) therapeutic dosages of islets and device encapsulation capacity; (iii) duration of effectiveness; and (iv) minimally invasive delivery.

CONCLUSION

All of the mHealth interventions that were presented were studied in RCTs, with the majority of interventions (eight out of 13) demonstrating clinically and statistically significant efficacy, and five interventions achieving null results or less than 0.5% (5.5 mmol/mol) difference in HbA1c reduction between intervention and control. These interventions range from advancements in glucose monitoring and insulin bolus calculators to health education and lifestyle changes. They consist of edifying material, self-monitoring, automated messages that encourage, educate, and provide feedback, as well as communication with a distant therapist via a telemedicine model. Personalized information, social support, and gamification are a few characteristics that could improve patient engagement; however, these have not been properly researched. More research is required to determine how individual aspects, such as health literacy, culture, socioeconomic position, habits, and treatment plan, affect patient engagement with mHealth technologies and clinical outcomes. This will enable more careful personalization of mHealth.

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