Injection Free Diabetes (Type 1) Management Using Implantable Device

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ABSTRACT

The prompt administration of first-aid drugs can save lives during medical emergencies such as anaphylaxis and hypoglycemia. However, administering these drugs, often requires needle self-injection, which can be difficult for patients under emergency conditions. As a solution, we propose an implantable device that is capable of administering first-aid drugs ondemand, such as epinephrine and glucagon, via a non-invasive, simple application of a magnet from the outside of the skin. This device is known as the implantable device with a magnetically rotating disk (iMRD).

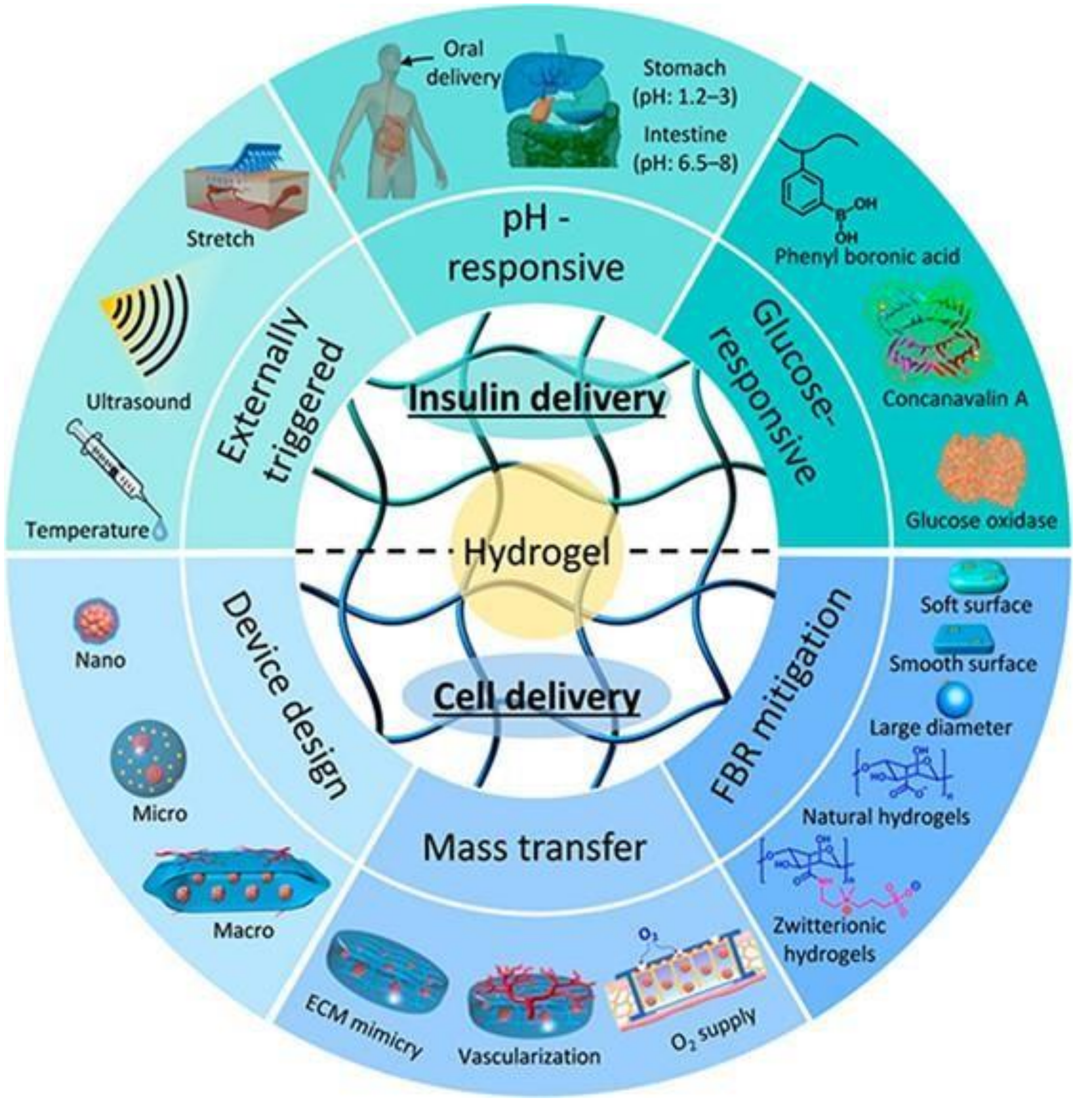
The iMRD contains a disk that is embedded with a magnet and multiple drug reservoirs that are sealed with a membrane. This membrane is designed to rotate at a precise angle only when the external magnet is applied. During this rotation, the membrane on a designated singledrug reservoir is aligned and torn to expose the drug to the outside.

When implanted in living animals, the iMRD can deliver epinephrine and glucagon, similar to conventional subcutaneous needle injections. This device provides a much simpler and efficient way of administering first-aid drugs during medical emergencies, especially for patients who are unable to self-inject.

Keywords: Compatibility, Implanted, Insulin, Materials, Rejection, Emergency Drug, Implantable Device, Magnetic actuation, Needle-free Drug Administration, On-demand Drug Administration.

INTRODUCTION

Type 1 diabetes mellitus (T1D) is an autoimmune disease that leads of the destruction of insulin-producing beta cells. Individuals with T1D require life-long insulin replacement with multiple daily insulin injections daily, insulin pump therapy, or the use of automated insulin delivery system. There is heterogeneity in the metabolic, genetic, and immunogenetic characteristics of T1D and age-related differences, requiring a personalized approach for each individual. Loss of insulin secretion can occur quickly or gradually. Residual insulin production is more common in adult-onset compared to youth-onset T1D, whereas diabetic ketoacidosis is more common in youth with T1D. Detectable c-peptide is associated with better glycemia control. The presence of other autoimmune conditions, obesity, comorbidities, and the development of diabetes-related complications is also variable.



People of all ages can develop type 1 diabetes. If you have type 1 diabetes, your pancreas doesn't make insulin or makes very little insulin. Insulin helps blood sugar enter the cells in your body for use as energy. Without insulin, blood sugar can't get into cells and build up in the bloodstream. High blood sugar is damaging to the body and causes many of the symptoms and complications of diabetes. Type 1 diabetes was once called insulin-dependent or juvenile diabetes, but it can develop at any age. In US 3.7 million people have diabetes. 1 in 5 don't know they have it. 96 million US adults over a third have prediabetes. More than 8 in 10 don't know they have it.

Type 1 Diabetes only accounted for an estimated10% of all cases of diabetes in the UK (Diabetes UK, 2009), but has serious short-and long-term implications and its incidence continues to increase worldwide. The condition has a strong genetic component, inherited mainly through the human leukocyte antigen (HLA) complex. The factors that trigger onset of clinical disease, however, remain unclear-although several theories exist (Manser et al, 1978; Rewers and Zimmet, 2004).

Diabetes is the eighth leading cause of death in the US (and may be underreported). In last 20 years, the number of adults diagnosed diabetes total $327 billion yearly. Medical cost for people with diabetes are twice as high as for people who don't have diabetes. Fewer than one in 10 people in the UK who have diabetes have type 1 diabetes. There is nothing you can do to prevent yourself or others developing type 1 diabetes. The exact causes are not known. Although it's often diagnosed in childhood, people can develop type 1 diabetes at any age. You are at a slightly higher risk of type 1 diabetes if your mother, father, brother or sister has it.

Some adults have a slowly progressive autoimmune destruction of their beta cells referred to as **Latent Autoimmune Diabetes of Adults or LADA**. Sometimes this is also known as diabetes type 1 ½. Individuals with LADA may be treated for years with diet and pills, and often are misdiagnosed as having Type 2 diabetes. Ultimately insulin replacement therapy is necessary to control the blood sugar. A diagnosis is made by confirming the presence of antibody markers.

You meet two criteria: the first, if there is no evidence in your blood that your immune system is attacking beta cells and the second, if you have alternating cycles where you need and then don't need insulin replacement. This form of the disease is unusual and most often diagnosed in those of African or Asian.

Type 1 diabetes is caused by a loss or malfunction of the insulin producing cells, called pancreatic beta cells. Damage to beta cells result in an absence or insufficient production of insulin production of insulin produced by the body. Most cases of type 1 diabetes have ab autoimmune basis, and the immune system mistakenly attacks and destroys beta cells. Since insulin is necessary to sustain life, the missing necessary to sustain life, the missing insulin has to be replaced. The replacement insulin is administered by injection using syringe or an insulin pump, which delivers the insulin under the skin.

Successful management of Type 1 diabetes requires multiple daily insulin injections (MDI), insulin pump therapy, or the use of an automated insulin delivery system, as well as glucose monitoring, preferably with a continuous glucose monitor (CGM). All people with Type 1 Diabetes should be able to perform capillary blood glucose monitoring (BGM) if CGM is unavailable. Self-management education, training, and support, as well as addressing psychosocial issues, help to optimize outcomes. A collaborative multidisciplinary approach, utilizing medical providers, nurse and dietitian educators, pharmacists, community resources, and specialists as needed (including podiatrists, mental health professionals, social workers, ophthalmologists, cardiologists, and other), is recommended.

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eye, kidneys and nerves. The most common is type 2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin. In the past 3 decades the prevalence of type 2 diabetes has risen dramatically in countries of all income level. Type 1 diabetes, once known as juvenile diabetes or insulin-little or no insulin by itself. For people living with diabetes access to affordable treatment, including insulin, is critical to their survival. There is a globally agreed target to halt the rise in diabetes and obesity by 2025.

About 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades.

DEVICES

There are some implantable devices for management of diabetes-

- Implantable device
- Blood glucose monitor
- Keton monitor
- Insulin pumps
- Smart insulin pens
- Continuous glucose monitor
- Diabetes management apps

1. Implantable Device:

This is a living medical device that is made from human cells that secrete insulin, along with an electronic life support-system. This is a new implantable device that not only carries hundreds of thousands of insulin-producing islet cell, but also has its own on-board oxygen factory, which generate oxygen by splitting water vapor found in the body. The device contains encapsulated cells that produced insulin, pulse a tiny oxygen-producing factory that keeps the cells healthy. This kind of device could also be adapted to treat other diseases that require delivery of therapeutic proteins.

It is a technique where the transplanted cells are protected from the host's immune system or tissue rejection by enveloping the cell in an artificial, partially permeable polymeric membrane which potentially allowed the grafting to the cells without using immunosuppressant drugs. Islets cell found in clusters (A number of cells grouped together) throughout the pancreas. They are made up of several type of cells. One of these is beta cells, which make insulin.

The blood ketone level is very heigh. You can get a ketone meter through your diabetes healthcare Team clinic or GP. If you're refused one from your GP because of the cost, ask your hospital-based Diabetes Healthcare Team to write to your GP to request a prescription. Most patient with Type 1 diabetes have to monitor their blood glucose level carefully and inject themselves with insulin at least once a day. However, this process doesn't replicate the body's natural ability to control blood glucose levels.

"The vast majority of diabetes that are insulin-dependent are injecting themselves with insulin, and doing their very best, but they do not have healthy blood sugar levels." If you look at their blood sugar levels, even for people that are very dedicated to being careful, they just can't match what a living pancreas can do."

A better alternative would be to transplant cell that produce insulin whenever they detect sugar in the patient's blood glucose levels. Some diabetes patients have received transplanted islet cells from human cadavers, which can achieve long-term control of diabetes; however, these patients have to take immunosuppressive drugs to prevent their body from rejecting the implanted cells.

More recently, researchers have shown similar success with islet cells derived from stem cells, but patients who receive those cells also need to take immunosuppressive drugs.

Another possibility, which could prevent the need for immunosuppressive drugs, is to encapsulated the transplanted cells within a flexible device that protects the cells from the immune system. However, finding a reliable oxygen supply for these encapsulated cells has proven challenging.

Some experimental devices, including one that has been tested in clinical trials, feature an oxygen chamber that can supply the cells, but this chamber needs to be reloaded periodically. Other researchers have developed implants that include chemical reagents that can generate oxygen, but these also run out eventually.

The MIT team took a different approach that could potentially generate oxygen indefinitely, by splitting, by spitting water. This is done using a proton-exchange membrane-a technology originally deployed to generate hydrogen in fuel cells-located within the device. This membrane can split water vapor (Found abundantly in the body) into hydrogen, which diffuses harmless away, and oxygen, which goes into a storage chamber that feeds the islet cells through a thin, oxygen-permeable membrane.

A significant advantage of this approach is that it does not require any wires or batteries. Splitting this water vapor requires a small voltage (about 2 volts), which is generated using a phenomenon known as resonant inductive coupling. A tuned magnetic coil located outside the body transmits power to a small, flexible antenna within the device, allowing for wireless power transfer. It does require an external coil, which the researchers anticipate could be worn as a patch on the patient's skin.

Drugs on demand:

After building their device, which is about the size of a U.S. quarter, the researchers tested it in diabetic mice. On group of mine received the device with the oxygen-generating, water-splitting membrane, while the other received a device that contained islet cell without any supplemental oxygen. The devices were implanted just under the skin, in mice with fully functional immune systems.

The researchers found that mice implanted with the oxygen-generating device were able to maintain normal blood glucose levels, comparable to healthy animals. However, mice that received the nonoxygenated device became hyperglycemia (with elevated blood sugar) within about two weeks.

Typically, when any kind of medical device is implanted in the body, attack by the immune system leads to a buildup of scar tissue called fibrosis, which can reduce the devices' effectiveness. This kind of scare tissue did from around the implants used in this study, but the device's success in controlling blood glucose levels suggests that insulin was still able to diffuse out of the device, and glucose into it.

This approach could also be used to deliver cell that produce other types of therapeutic protection that need to be given over long periods of time. In this study, the researchers showed that the device could also keep alive cells that produce erythropoietin, a protein that stimulates red blood cell production.

"There are a variety of diseases where patients need to take proteins exogenously, sometimes very frequently. If we can replace the need for infusions every other week with a single implant that can act for a long time, that could really help a lot of patients."

The materials used are inherently stable and long-lived, so that kind of long-term operation is within the realm of possibility.

Study points a way to better implants:

Medical device implanted in the body for drug delivery, sensing, or tissue regeneration usually come under fire from the host's immune system. Defense cells work to isolate material they consider foreign to the body, building up a wall of dense scar tissue around the devices, which eventually become unable to perform their functions.

A signaling molecule that is key to this process of "fibrosis," and they have shown that blocking the molecule prevents the scare tissue from forming. This gives us a better understanding of the biology behind fibrosis and potentially a way to modulate that response to prevent the formation of scar tissue around implants.

Preventing fibrosis:

Implantable device that could mimic the function of the pancreas, potentially offering a long-term treatment for diabetes patients. The device encapsulates insulin-producing islet cells within a material called alginate, polysaccharide naturally found in algae. Alginate provokes a lesser immune response than human-made materials such as metal, but it still induces fibrosis.

Information about the device:

A potential method of managing Type 1 diabetes is the transplantation of pancreatic islet cell capable of producing insulin. This could help eliminate the need for regular insulin shots. The downside is that these cells eventually get depleted of oxygen, halting their insulin production. To address this issue, engineers have created a new implantable device that not only houses hundreds of thousands of these insulin-making islet cells but also contains its own mechanism for producing oxygen by splitting water vapor found naturally in the body.

In order to develop the implantable device, the team of engineers at MIT (Cambridge, MA, USA) used a novel method aimed at limitless oxygen generation by splitting water. The key element inside the device is a proton exchange membrane, a technology initially developed for hydrogen production in fuel cells. This membrane separates the water vapor in the body into hydrogen, which safely diffuses, and oxygen, which is stored in a chamber that feeds the islet cell via a thin, oxygen-permeable membrane. The team is now considering scaling up the device to the size of a chewing gum stick for trials in people with Type 1 diabetes.

In tests involving diabetic mice, the device was able to maintain stable blood glucose levels for a during of at least one month. Implanting medical devices usually result in the immune system creating scar tissue, known as fibrosis, which can impair the device's function. Although scar tissue did from in this study, the device remained effective in regulating blood sugar level, suggesting that insulin was still able to flow out and glucose to flow in. While diabetes treatment remains their primary goal, the researchers believe the technology could be modified to manage other conditions requiring continuous delivery of therapeutic proteins.

The device, described as a "living medical device," combines human cells that produce insulin with an electronic life support system. It has the potential to revolutionize diabetes treatment by mimicking the body's natural ability to control blood sugar levels.

Current diabetes management involves daily insulin injections, but this method often falls short in achieving healthy blood sugar levels. Transplanting islet cells from human cadavers or stem cells has shown promise, but patients require immunosuppressive drugs to prevent rejection.

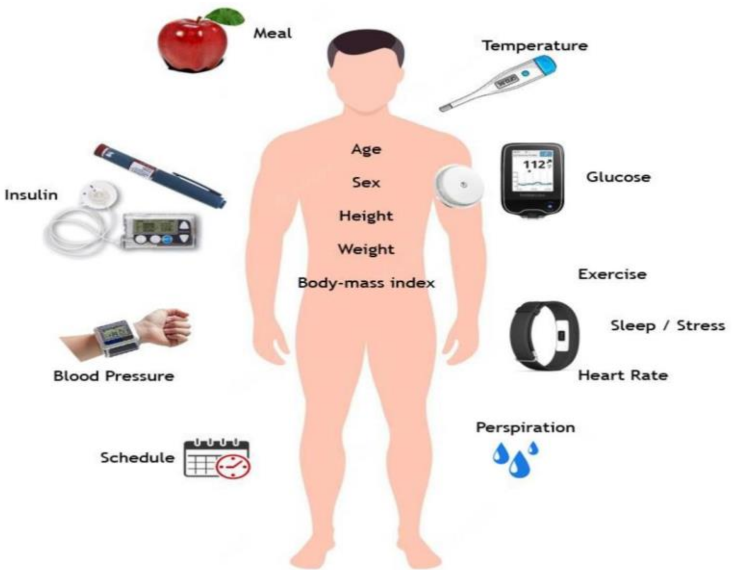
MIT's device offers a promising solution. It encapsulates islet cells within a flexible device, protecting them from the immune system. Unlike previous attempts, this device doesn't require external reloading of oxygen chamber or chemical reagents.

Wireless power transfer, using a small voltage generated through resonant inductive coupling, supplies power to the device through a magnetic coil placed externally on the patient's skin. In mouse trials, the device with oxygenated version led to hyperglycemia within two weeks.

Though scar tissue formed around the implants, the device remained effective in controlling blood glucose levels, suggesting insulin diffusion continued. Beyond diabetes treatment, this approach could deliver other therapeutic proteins over extended periods.

The team's goal is to develop living medical devices that reside in the body and produce drugs as needed, potentially transforming treatment for various diseases. MIT's groundbreaking research offers hope for a new approach to treating not only diabetes but also other conditions requiring long-term therapeutic protein delivery.

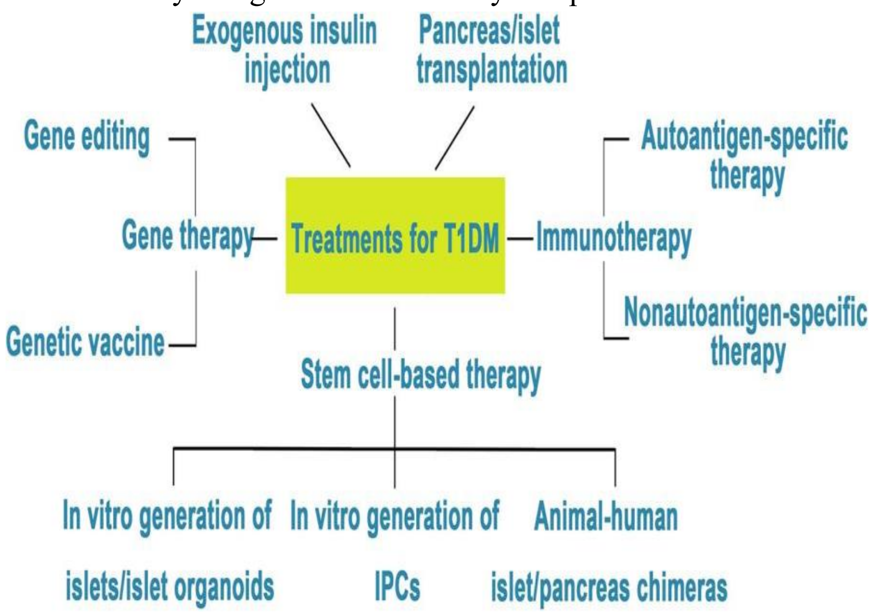
Target approach:



Other implantable devices whose functions can be disrupted by fibrosis include glucose sensors for diabetics, pacemakers, and any other devices that need to interact with surrounding tissue.
This targeted approach holds the potential to be safer than another strategy that some researchers have tried, which is widespread suppression of the immune system. “If you use a broad-spectrum drug, you may be getting rid of cell types that are important for reducing fibrosis or even for other vital immune functions in the body-wound healing or fighting off parasites, bacteria or viral infections. This is one of the first studies to really examine the fundamental of how the immune system interacts with implantable biomaterials.

Methodology:

- Receiving insulin producing islet cell from human cadaver.
- Using it is implanting device and onboard oxygen chamber.
- Oxygen chamber dies not require any battery or wire.
- It splits water vapours using Resonate inductive Coupling.
- Human Body contain about 60%.
- For Splitting the water vapour, it requires small 2volt current using RIC.
- **RIC:** A tuned magnetic coil located outside the body, body transmits power to flexible antenna on implants, allows wireless power transplant. It requires external coil which can be anticipated as wearable patch on skin.
- FBR (Foreign Body Response): When any foreign body or implant used, the immune system generated response and cause of fibrosis.
- To avoid such conditions the biocompatible (polymers: Silicon, Polyethene or gold, platinum) used.
- Mainly fibrosis is avoided by using anti-inflammatory compounds.



Frequent insulin injection are an unpleasant, albeit necessary reality for many patients with type 1 diabetes. However, new technology could create a different reality for these patients by treating the disease in one fell swoop.
Implantable device that could provide a long-term supply of insulin to the body. The implant was designed to shield insulin-producing, or islet, cell from damaging immune responses, while continuously generating oxygen to sustain them. The result of a study in the Proceedings of the Nation Academy of Sciences show

that transplanted cell within the device were able to survive and produce insulin in animal over the course of one month.

With type 1 diabetes, the immune system turns on the body, destroying islet cells within the pancreas and hindering the body's ability to produce insulin, a hormone that regulate blood sugar. Standard treatment typically requires patients to inject insulin several times a day, but researchers have sought a longer lasting solution that is less physically and mentally taxing on patients-replacing the destroyed islet cells.

Despite recent progress, transplanting islet remains a significant challenge. These cells need protection from the immune system, and while immunosuppressive medications can stave off hostile attack, these drugs are not suitable for all patients as they can elicit severely adverse reactions. Encapsulating cell within implantable device is another strategy, but this protection can also cells off from oxygen, ultimately causing islets to die.

In the new study, the authors hatched a plan to make oxygen available on the spot for encapsulated cell using another ample resource in the body-water.

Their bioelectronic prototype implant, which is roughly the size of quarter, features an electrode that sends electric current through nearby water molecules, splitting them into hydrogen and oxygen. Below the electrode, chambers housing islet cells are encapsulated in oxygen-permeable membrane, allowing the oxygen to reach them.

To maintain a lean, wireless design, the researchers built the device without a battery on board. Instead, an external power source emits radio waves that are picked up by a receiver on the device, generating electrical current. The process, known as inductive coupling, is commonly used to wirelessly charge smartphones and other devices.

The authors tested their strategy by loading devices with islet cells from rats and implanting them into a diabetic mouse model. Over the course of a month, they measured blood sugar levels in the treated mice, which decreased to normal levels within a day and held there until two days after implants were removed. In a separate experiment, the team injected a high dose of glucose into the diabetic mice, spiking their blood sugar levels. Like in healthy mice, the mice with the implant produced enough insulin to quickly their blood sugar to a healthy level. This initial success in mice sets the team up for future work in large animal for longer stretches of time. These next steps will entail packing more cells into the implant while keeping the overall size of the implant small.

"This device tackles a cohort of challenges researchers have contended with for a long time". "This research has the potential to one day reduce the burden of constant insulin management for patients and may also provides treatments for other disorders."

2. Blood Glucose Monitor:

Blood glucose monitors or glucometers are handly devices that measure a person's blood sugar level from a small sample, usually from a fingertip. Glucometer kits come with lancets that people use to prick their fingers to obtain a blood sample. They run the test by inserting the strip into the monitor showing their current blood sugar level. Glucose in the patient's blood sample rehydrates and react with the enzyme to produce a product that can be detect.

The detector portion of the meter is composed of electronics, so it must also be protected from extremes of temperature, humidity, moisture, and the elements. Many meters now have internal temperature checks that prevent use of the meter outside of acceptable tolerance by blocking patients results or displaying an error code if the ambient conditions of temperature and humidity are outside manufacturer ranges. Glucose meters must also not be submerged in water when cleaning and must also be protected from moisture, as with any electronic device.

3. Ketone Monitor:

A Blood Ketone meters are devices that allow you to test, for ketones circulating in your body. These are chemicals produced by the liver when the body needs to burn fat as fuel. Everyone has ketones and they're normally not a health concern. It measures the ketones in your blood glucose meter measure glucose. In fact, blood ketone meters and blood glucose meters look very similar and after combined into one device. They are just measuring different things.

Lower than 0.6 is a normal reading for blood ketones. 0.6 to 1.5mmol/L means you're at a slightly increased risk of DKA and you should test again in two hours. 1.6 to 2.9mmol/L means you're at an increased risk of DKA and should contact your Diabetes Healthcare Team or GP as soon as possible. 3mmol/L or above means you may be in DKA and should get medical help immediately.

Ketones are type of chemical that your liver produces when it breaks down fats. High levels of ketones in your blood or urine can mean you're at risk of developing diabetic ketoacidosis. This can be life-threatening, so it's important to be aware of your ketone level. If you don't have enough insulin, you'll start to use fat for energy. And when you use fat for energy your liver starts to produce ketones.

4. Insulin Pumps:

An insulin pump is a small device that delivers insulin through a small plastic tube (catheter). The device pumps insulin continuously day and night. It can also deliver insulin more rapidly (bolus) before meals. Insulin pumps can help some people with diabetes have more control in managing blood glucose.
Most insulin pumps are about the size of a small mobile phone, but models keep getting smaller. They are mostly worn on the body using a band, belt, pouch, or clip. Some models now are wireless. Traditional pumps include an insulin reservoir (cartridge) and a catheter. Patch pumps are worn directly on the body with the reservoir and tubes inside a small case. A separate wireless device programs insulin delivery from the pump.
An insulin pump delivers insulin continuously to the body. Except in rare circumstances, the device usually uses only rapid-acting insulin. It can be programmed to release different doses of insulin based on your blood glucose level.

5. Smart Insulin Pens:

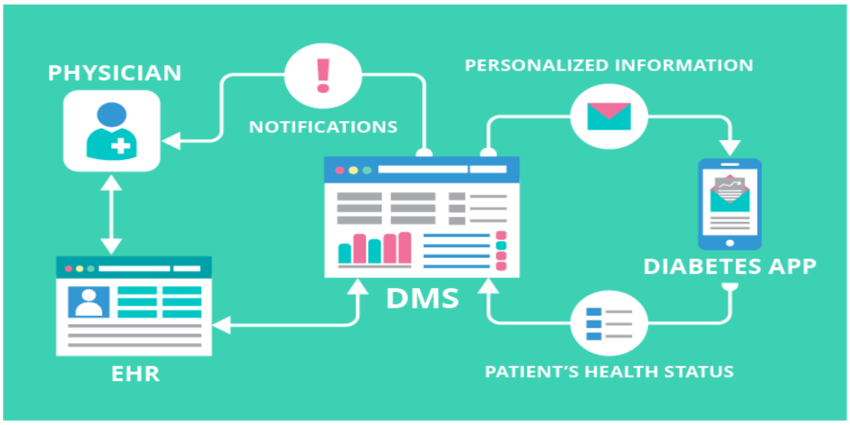
The first Food and Drug Administration (FDA)-cleared reusable smart insulin pen was launched in 2017. Smart pens are designed to be smartphone and paired it with your pen, you're ready to go. The device sends real-time data to the app via Bluetooth connection.
A smart insulin pen is a reusable injector pen with an intuitive smartphone app that can help people with diabetes better manage insulin delivery. This smart system calculates and tracks doses and provides helpful

reminders, alerts, and reports. They can come in the form of an add-on to your current insulin pen or a reusable form which uses prefilled cartridges instead of vials or disposable pens.
Smart insulin pens are a rapidly growing market. Because they are typically more affordable, easy to use, and offer many benefits and improvements for people who depends upon insulin to manage their diabetes.

6. Continuous Glucose Monitor:

Continuous glucose monitoring means using a device to automatically estimate your blood glucose level, also called blood sugar, throughout the day and night. A continuous glucose monitor (CGM) estimates what your glucose level is every few minutes and keeps track of it over time.
A CGM has three parts. First, there is a tiny sensor that can he inserted under your skin, often the skin on your belly or arm, with a sticky patch that help it stay there. These sensors are called disposable sensors. Another type of CGM sensor- called an implantable sensor-may be placed inside your body. CGM sensors estimated the glucose level in the fluid between your cell, which is very similar to the glucose level in your blood. Sensors must be replaced at specific times, such as every few weeks, depending on the type of sensor you have.
The second part of the CGM is a transmitter. The transmitter sends the information, without using wires, to the third part, a software program that is stored on a smartphone, on an insulin pump, or on a separate device called a receiver.

7. Diabetes Management Apps:



Many people living with diabetes may find that keeping track of their diet, physical activity, and blood glucose levels can be difficult to manage. Luckily, there are many smartphone apps available that can make managing your diabetes easier. These apps assisted you in achieving your diabetes self-management goal by providing easyto-use platforms that take some of the 'guesswork' out of activities like food tracking or blood glucose monitoring. This factsheet details some of the most useful apps for diabetes self-management support found in the App Store on iOS devices and Google Play Store on Androids.

Diabetes Management Apps:

a. Blood Sugar Monitoring
b. Glucose Buddy
c. One Drop
d. MySugr
e. Diabetes:M
f. Dario Health
g. Sugarmate
h. Feelmo
i. Hector: Depression Self Help
j. being: my mental health friend
k. Bezzy T2D
l. CalorieKing
m. Carb Manager
n. My FitnessPal,
o. Fooducate
p. MyPlate Calorie Counter
q. MyNetDiary
r. Nike Training Club: Fitness
s. Walk at Home
t. Google Fit
u. Walkr
v. Yoga For Weight Loss and fitness

Monitoring and treatment of diabetes often involves a variety of connected devices such as blood glucose monitors, CGMs, insulin pumps, and other wearable sensors.

CONCLUSION

It concludes that combined diet and physical promotion programs are cost-effective, and recommends such interventions for individual at increased risk for developing type 2 diabetes based on "strong evidence of effectiveness in reducing new-onset diabetes." If left untreated, diabetes can cause serious health complications, such as nerve damage, kidney disease, and blindness. Therefore, it is essential to seek medical attention if you experience any symptoms of diabetes.

Insulin delivery:

- Insulin Pen
- Insulin Pump -Conventional pump-Patch pump Glucose Sensing:
- Capillary blood glucose
- Continuous glucose monitoring

- Flash glucose monitoring
- Conventional
- Implantable

Data Management:

- Health-care professional-centred
- Data and/or web portals • Patient-centred
- Data and/or web portals
- Remote monitoring
- Mobile app

Glucose-responsive Insulin Delivery:

- Threshold-based suspension
- Predictive low-glucose suspension
- Hybrid single-hormone closed-loop

As daunting as the aforementioned technical, business, and regulatory challenges may be, the growing need for effective long-term diabetes management and the concomitant opportunities that such need creates continue to generate considerable activity on the part of researchers and developers. Through ever more advanced technologies providing long -term solutions, clinical and patient alike can look forward to an improved quality of life and effectively pain-free management of their underlying condition.

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