

**REVIEW OF NEW TECHNOLOGIES FOR THE MANAGEMENT OF DIABETES
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ABSTRACT

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), it is one of the leading causes of death in the world. Type-II Diabetes (ineffectiveness of insulin) is the most common when compared to the Type-I diabetes, once known as juvenile diabetes or insulin-dependent diabetes (lack of insulin), About 420 million people worldwide have diabetes particularly in low and middle income countries, the prevalence of diabetes has been steadily increasing for past 3 decades. Recently the technology expanded to hybrid devices which can monitor glucose levels and deliver insulin if there is any abnormality present in the insulin. The idea of automated “closed loop” systems for pairing CGM (Continuous Glucose Monitoring) devices and insulin pumps are considered for diabetes management as a next level. Now a day’s Insulin in pumps are ready to use to overcome the Diabetes. Diagnostics have the potential to make diagnosis and treatment of diabetes simple and cost effective as well as patient friendly. Use of telemedicine and electronic medical records represents a significant advance in improving delivery of diabetes care and monitoring of its therapeutic outcomes. We summarize the technologies use for the management of diabetes and review focuses on continuous glucose monitoring devices, insulin pumps, and getting clinicians connected to technologies. The technology concerns, ongoing development and future trends in this area are also discuses.

KEYWORDS: Diabetes technology, New Technologies, Continuous glucose monitoring, Insulin pump.**INTRODUCTION**

Diabetes mellitus (DM) is a group of metabolic diseases that affect the body’s ability to regulate blood glucose levels. In Type 1 DM (T1DM), the immune system attacks the insulin producing pancreatic cells resulting in absolute deficiency of insulin secretion, while Type 2 DM (T2DM) is characterized by increased resistance of the body cells to insulin, which frequently coexists with limited insulin secretion. T2DM is often progressed from prediabetes, which is classified into impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). In the IFG condition, the fasting blood glucose is elevated above the normal levels, while IGT is a prediabetic stage of dysglycemia. Both IFG and IGT are associated with insulin resistance and increased risk of cardiovascular disease.

VARIOUS TYPES OF DEVICES USED IN DM**I. Blood Glucose Monitoring Devices**

Optimal diabetes management relies on accurate glucose monitoring devices. Advances in blood glucose (BG) monitoring technology have resulted in improved accuracy, smaller required blood volumes, and the ability to transfer data between the BG meter and insulin delivery devices.

A. Capillary blood glucose monitoring**Devices**

Current home BG meters use capillary blood samples ranging from 0.3-1.5 microliters. The sample is analyzed using either a glucose oxidase or a glucose dehydrogenase reaction. Some strips use the enzymatic/biosensor reaction alone, while others convert the enzymatic reaction into an electrochemical signal first. Although whole blood is used, the meter output is calibrated to provide results that correlate with plasma glucose values. Subtle differences exist among meter performances, such as the ability to withstand temperature extremes and accuracy at higher altitudes. Additionally, certain substances interfere with test strip accuracy. An altered hematocrit will falsely alter the BG in the same direction. Maltose, ascorbate, and acetaminophen interfere with the enzymatic reaction on the test strip, greatly affecting the accuracy of the BG reading. A combination of interfering substances can have up to a 193% impact on the accuracy of the BG reading. Despite slight variations in meter advantages, all of the currently FDA approved meters are within 10-15% of actual laboratory plasma glucose values. A reference table of currently available BG meters is published by Diabetes Health every January.^[1]

1. Enhanced devices

Meter capability is continuously being enhanced. The Freestyle InsuLinx, approved in Europe in 2011, allows patients to program their insulin-to-carbohydrate ratio, correction factor, and target BG into the meter. This information enables the meter to recommend the next insulin dose based on BG and carbohydrate intake. A simplified version of the Freestyle InsuLinx, FDA approved in March 2012 and available for use in the US, works as a meter with a touch screen electronic logbook without bolus calculation capabilities. The One Touch Verio IQ meter, approved in the US and Canada in February 2012 recognizes patterns of hypo- or hyperglycemia and alerts the user to them.^[1,2]

2. Cell phone-enhanced meters

The LG KP8400 cell phone add-on has been available in Korea since 2002, and the Infopia LG Glucophone/JVAGO 5965 has been advertised for the US market since 2008. The meter piece is attached to the back of the phone, near the battery pack. Readings are displayed on the cell phone and can be uploaded to an online database. This device is currently unavailable in the US. The European, Bluetooth-enabled GlucoTel system enables wireless transmission of glucose values from a BG meter to a web-based logbook using the individual's mobile phone as the communication hub. The iBG Star meter and app, recently developed by Sanofi-Aventis, allows certain smartphones (iPhone or iTouch) to serve as the BG meter.^[2]



3. Plug-and-play devices

The iBG Star meter is one type of plug-and-play device, as the meter must be plugged into a smartphone in order to function. The smartphone serves as this meter's screen. Another type of plug-and-play device is the Ascensia Contour USB meter, which is a blood glucose meter that also has a USB drive and contains software within it so BG data can be downloaded to a computer without the need of additional software/cables.^[2]

4. Combination devices

In the past, Novo Nordisk partnered with Lifescan and created a device called the InDuo, which was the world's first combined BG meter and insulin delivery device. The meter debuted in 2002, and for undisclosed reasons was discontinued in 2006.^[10] BG meters that double as remote controls for insulin pumps are currently available (see below). After a several year hiatus, BG

meter/insulin delivery combination devices are now being revisited.^[3]

5. Communication with other devices

Radiofrequency technology is used to transfer BG data to insulin pumps; all currently available insulin pumps are enabled with this feature. The Medtronic Mini Med pumps' associated meters (One Touch UltraLink and Ascensia Contour next link) send BG values to the pump to be incorporated into the calculation of the insulin dose. The Animas One Touch Ping, OmniPod PDM, and Accu-Chek Aviva Combo meters serve as the remote control to the pump itself. The Animas Vibe and Medtronic MiniMed Paradigm systems receive information from their paired real-time continuous glucose monitoring transmitters and display the information on the pumps screen.^[1]

B. Continuous glucose monitoring (CGM)

Basic CGM

Real-time continuous glucose monitoring (RT-CGM) allows for continuous measurement of interstitial glucose concentrations. A small, enzyme-coated filament (<13 mm in length) inserted subcutaneously detects interstitial glucose through a glucose oxidase reaction. The electrochemical signal is transmitted to a receiver using radiofrequency, where it is converted into a glucose value. The receiver can be an insulin pump (Medtronic Paradigm system, Animas Vibe system) or it can be a stand-alone unit (DexCom, Freestyle Navigator, Medtronic Guardian). The Medtronic's iPro is a blinded system used by clinicians for diagnostic or research purposes. Sensor glucose values are updated every 1–5 minutes. Sensor electrodes can remain in the body for 3–7 days.

RT-CGM systems must be calibrated at regular intervals with a fingerstick BG value, both for accuracy and in order to continue giving the user information. Sensor glucose values are generally within 20% of actual BG values.^[1,2,3]

Benefits

RT-CGM is clinically useful in identifying post-prandial hyperglycemia, overnight hypoglycemia, hypoglycemia in those with hypoglycemia unawareness, and daily glucose trends. Studies show that patients with type 1 diabetes who use RT-CGM at least 60-70% of the time have significant improvements in glycemic control. A recent study found sensor use even 41-60% of the time to have beneficial glycemic effects. Early studies found that patients who are at least 25 years of age experienced the greatest benefits from RT-CGM use. This was hypothesized to be due to increased RT-CGM use and better adherence to treatment in adults compared with children and adolescents. Newer studies have shown glycemic benefits of RT-CGM in all age groups. In a sample of pediatric patients, Ramchandani et al. found that although only 21% of all subjects who had a sensor used it continuously, 76% of subjects who owned a

sensor believed that using RT-CGM helped them to better manage their diabetes.

Disadvantages

The difficulty with RT-CGM is getting patients, especially children and adolescents, to use it on a regular basis for extended periods of time. In many, the frequency of RT-CGM use decreases over time, especially when patients experience frustration with the system. The major reasons cited for disuse of RT-CGM are that patients found it annoying, a hassle, and interfering with their lives. Those who stop using it do so because of problematic equipment, insurance issues, and inaccuracy. These issues need to be addressed before RT-CGM is embraced more universally.

Connecting CGM to clinicians

Current CGM devices can be uploaded into device-specific software programs and shared with clinicians either as PDF or Word documents (attached to an e-mail or sent by fax), as web-based reports (Medtronic MiniMed CGM devices only), or during an office visit. Glucose sensors can only be downloaded by proprietary programs, and CGM data fails to integrate with electronic medical record databases.

Future directions/under development

The goal of RT-CGM is to develop smaller, more accurate devices. Technologies under consideration include an enhanced transdermal system (Symphony tCGM), multiple optical sensors using impedance spectroscopy, an optical fluorescence fiber-optic biosensor using fluorophore-labeled glucose/galactose binding protein technology which is shown to be >95% accurate *in vitro*, non-enzymatic glucose sensors based on nickel (II) oxide electrospun nanofibers and nickel nanoparticles on carbon nanotubes, and a small (3.6 mm x 8.7 mm) continuous osmotic injectable/implantable glucose sensor whose performance is reliable *in vitro* for up to four weeks. Additionally, intravascular glucose sensors for use in the critical care setting in the hospital are in the works. More accurate RT-CGM devices are needed and have great potential for use both with and without an artificial pancreas.^[1]

Connecting CGM to insulin delivery, including closed-loop

Some insulin pump companies have already connected glucose sensors to insulin delivery devices in the first steps towards an artificial pancreas. The Medtronic MiniMed Veo pump, available in Europe, Australia, and Canada, suspends basal insulin delivery for two hours if the sensor glucose is below a set level and the individual with diabetes fails to respond or the sensor glucose remains low for a given amount of time. Two insulin pump/glucose sensor devices are currently approved for patient use and many more are currently under development. The Juvenile Diabetes Research Foundation (JDRF)'s proposed steps towards development of the artificial pancreas include: 1) a

sensor-augmented pump that will shut off for a specific amount of time when the user does not respond to a low glucose alarm, 2) a hypoglycemia minimizer that adjusts insulin delivery when a low glucose is predicted, 3) a hypoglycemia and hyperglycemia minimizer that will decrease insulin delivery if a low glucose is predicted and increase it if a high glucose (e.g., >200 mg/dl) is predicted, 4) a hybrid closed loop, where the user manually assists the system by bolusing for food intake, 5) a fully automated closed loop with insulin only, and 6) a fully automated multi-hormone closed loop system. Currently, Step 1 is commercially available in Europe, Australia, and Canada (the Medtronic Veo system), and Steps 2–6 exist in research studies.

II. INSULIN DELIVERY DEVICES

A. Insulin pumps

Insulin pumps are the most physiologic means currently available for insulin delivery. Advancements in technology have transformed what in 1964 was once a large piece of equipment to a small, beeper-sized device that delivers both basal and bolus insulin. User input is essential for a pump to function optimally.^[1,2,3]

Today's pumps are available in both wired (with external tubing, e.g., Animas, Medtronic MiniMed, Roche) and wireless (without external tubing, e.g., OmniPod) versions. The wired pumps are attached to the body using an infusion set. The current wireless (patch) pumps are about the size of a small computer mouse, and are attached directly to the body without any tubing in between. A small catheter is inserted subcutaneously from the underside of the patch pump by pressing a button on the remote control. This serves as the patch pump's infusion set. Today, basal rates can be titrated in as small as 0.025-unit increments, and boluses can be given in 0.05-unit increments. Wired pumps can be detached from the site for showers, water sports, and other activities. Currently available patch pumps remain on the body and are waterproof.



Existing insulin pumps allow the user to enter their carbohydrate intake and their BG, and the pump calculates the insulin dose based on their settings. Medtronic MiniMed and Animas both have sensor-augmented pumps available, wherein interstitial glucose readings are checked every five minutes and displayed on the pump's screen. The Medtronic MiniMed Veo, which is only available outside of the US, has an auto-

shutoff feature if the sensor glucose is low and the user does not respond.

Benefits

Many studies have found better glycemic control and/or better quality of life in patients who use insulin pumps compared to those on multiple daily injections (MDI). However, other studies have failed to show improvement in glycemic control compared to MDI. Even without improvements in glycemic control, the quality of life benefits offered by insulin pump therapy are worthwhile. Insulin pumps are easy to use in insulin-requiring patients of all ages, including infants.

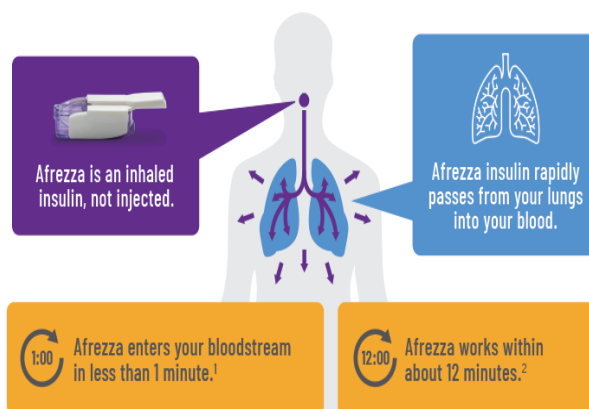
Sensor-augmented pumps improve glycemic control, but only when the sensor is worn at least 41-60% of the time. Both adult and pediatric patients with diabetes have attained metabolic benefits using these devices.

Disadvantages

The biggest potential downside to insulin pump therapy is being tethered to a device, and the fact that the presence of this device is a constant reminder that one has diabetes. However, few patients discontinue insulin pump therapy because of these issues. Rapid onset of ketoacidosis (DKA) can occur within 7–8 hrs with insulin pump therapy if there is an infusion set or insulin delivery malfunction because there is no long acting insulin to provide a safety net as with MDI.

B. Inhaled insulin

Inhaled insulin formulations have been under development for several years, and existing products are able to mimic both first- and second-phase insulin responses. Pfizer's Exubera was available in the US market for approximately six months, but it was unsuccessful and was discontinued due to large, difficult to titrate volumes that needed dispensation by a large device. Other formulations of inhaled insulin are in the works, and their absorption and action profiles are excellent. Limitations of inhaled insulin include difficulty titrating the exact dose needed, potential absorption issues through alveolar and/or buccal membranes, the size of the insulin delivery device itself, and the potential of repeated insulin dosing causing hypertrophy or other problems in the lungs. Additionally, basal insulin must still be injected despite the use of inhaled insulin.



C. Insulin pills

Insulin is a protein which is degraded by digestive enzymes and hence must be taken as an injection. However, by using different sized particles, coverings, and inhibitors which allow for insulin to be transported through the gastrointestinal tract, a few companies have developed an insulin pill that is taken by mouth and works like an injection of quick-acting insulin. Limitations of this preparation include that the pill must be taken on an empty stomach for proper absorption. Additionally, if the patient has a second helping of food, the second dose of the insulin pill is not effective because the food that is already in the stomach prevents its absorption. Insulin pills are not yet FDA approved.



D. Insulin patches/Transdermal insulin delivery

Transdermal insulin delivery allows insulin to be absorbed through the skin and can be given anywhere on the body, regardless of the body composition of the person with diabetes. Insulin patches can be potentially used with both rapid-acting and long-acting insulins. However, no matter which insulin is put into the patch, all insulin patches have worked like basal insulin until recently. Insulin patches are not yet commercially available.



E. Smart insulin

Initially a creation of a nanotechnology scientist from MIT and now being developed by Merck, SmartInsulin is an insulin that has been chemically modified to release insulin in response to glucose in the bloodstream. The chemical component attached to the insulin, a biodegradable polymer containing sticky sugar groups, causes it to remain insoluble in the body until a certain concentration of glucose is reached. The glucose then attracts the components that make the insulin insoluble, pulling them away from the hormone and allowing it to become active. It is believed that this will allow for better postprandial insulin coverage while minimizing the incidence of hypoglycemia, all with only one injection per day. SmartInsulin is still in preclinical studies.^[1,2,3,4,5]

DISCUSSION AND CONCLUSION

Finally we conclude that the optimal diabetes management relies on accurate glucose monitoring devices. Advances in blood glucose (BG) monitoring technology and insulin delivery devices have resulted in improved accuracy. They are two types of BG monitoring devices they are capillary blood glucose monitoring, continuous glucose monitoring connected to insulin delivery devices. Capillary blood glucose monitoring devices includes enhanced devices, cell phone enhanced meters, plug and play devices, combination devices, communication with other devices. real time continuous glucose monitoring (RT-CGM) for continuous measurement of glucose concentrations connected to insulin delivery devices like insulin pumps, inhaled insulin, insulin pills, insulin patches/transdermal insulin delivery, smart insulin. BG meters published by diabetes health every January approved by FDA among those freestyle InsuLinx was approved by FDA in March 2012. Cell phone enhanced meters like LGKP8400 cell phone available in Korea since 2002 the iBG star meter serve as the BG meter it is a type of plug and play device. BG meter/insulin delivery combinations also available. Insulin pumps used for insulin delivery these studies have found better glycemic control and better quality of life in patients who use insulin pumps compared to multiple daily injections. Insulin pumps use in requiring patients of all ages including infants. Among insulin delivery devices insulin pills are not yet approved by FDA, insulin patches are not yet commercially available, Smart Insulin is still in preclinical studies. We are in the midst of a revolution of technological advancements in diabetes care. This technology boom

and associated variety of diabetes management tools enable clinicians to develop new and innovative means of treating their patients. Additionally, these advancements have the potential to decrease the burden of diabetes management on the patients themselves. Advances in diabetes technology will continue to improve patient care and its delivery, and may one day lead to fully automated treatment systems for people with diabetes mellitus. As a clinical pharmacist we suggest to the physicians kindly adopt various new technologies for treating Diabetes for improve the better therapeutic and quality of life to the patient. In this technologies are very cost effective so whom they are having low income that patient's are not bearing for this treatment.

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