Current Status of Diabetes Technology

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INTRODUCTION

Type 1 Diabetes (T1D) has affected humans for thousands of years, and descriptions of diabetes symptoms appeared in ancient Greek and Egyptian writings. Until the discovery of insulin in 1921 by Banting and Best, T1D was a terminal diagnosis, fatal within one year, but currently nearly 200,000 Americans under the age of 20 years are living with T1D.

For much of the 20th century, T1D treatment consisted of two injections daily of insulin derived from beef or pork in a combination of short-acting (regular) and longer acting (NPH) forms. Other than by phlebotomy, hyperglycemia could only be detected if the blood sugar exceeded the renal threshold for glucose.

Home blood glucose monitoring did not begin until the 1970s, 50 years after insulin was first discovered. It was not until the early 1990s that the landmark Diabetes Control and Complications Trial (DCCT) confirmed irrefutably that better control of blood glucose significantly reduced the rate of chronic complications associated with T1D.[1] After the publication of the DCCT, the goal of diabetes management became optimal blood glucose

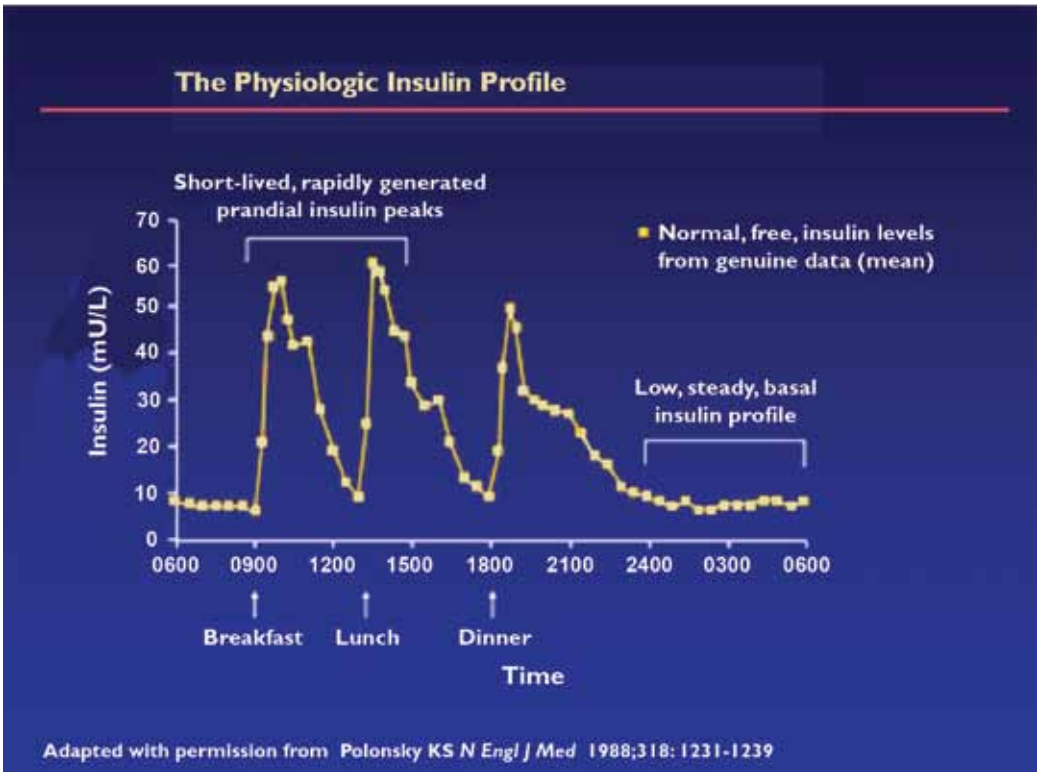

Fig. 1. Twenty-four hour profiles and pulsatile pattern of insulin secretion.
Polonsky, KS. *J Clin Investigation* 1988 Feb; 81 (2) 442-448

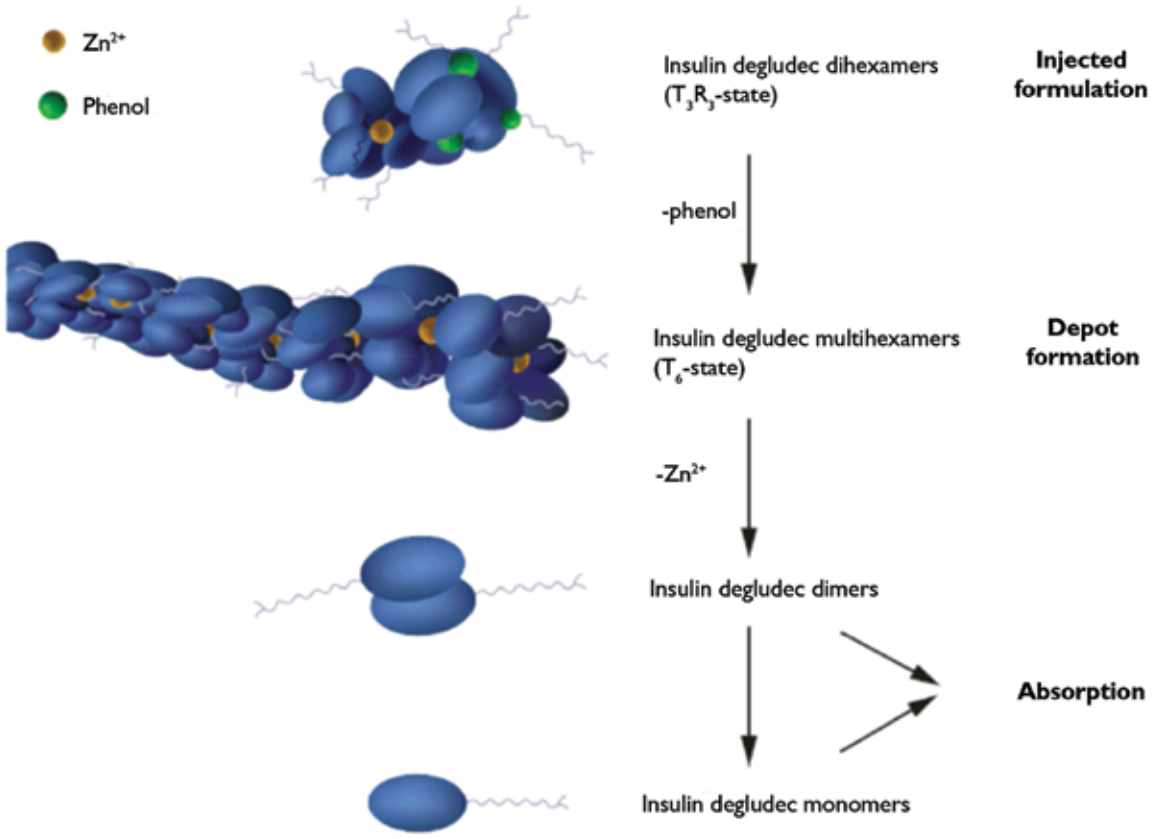

Fig. 2. Design of the Novel Protraction Mechanism of Insulin Degludec
Jonassen I, et al. *Pharm Res* (2012) 29:2104-2114

control, with insulin replacement formulated to be as close to physiological as possible without causing severe hypoglycemia. The DCCT findings thus led to rapid changes in insulin products, insulin delivery systems, and the methods of home blood glucose monitoring. In the 21st century, technological changes have further advanced our ability to achieve near-normal blood glucose levels.

DIABETES TECHNOLOGY

This term encompasses the devices, hardware, and software used to manage blood glucose levels, reduce the burden of living with diabetes, and improve the quality of life. Diabetes management through technology changed dramatically with the advent of computer software and applications, Bluetooth connectivity, and "closed loop" systems. The latter are hybrid devices, which both monitor glucose levels and deliver insulin, with the capability of automatically adjusting insulin delivery based on glucose data through the use of algorithms. This is a rapidly changing area. Below is a summary of the latest technological advances in insulin, insulin delivery, and glucose monitoring.

INSULIN

In the 1980s, recombinant DNA technology led to the production of human insulin. Steady advances have led to analogs of human insulin in use today that have a quicker onset of action and more rapid peak effect than traditional synthetic "regular" insulin, allowing dosing that is more physiologic (Fig. 1). Analog rapid-acting insulin is used in insulin pumps.

Analog human basal insulin in use today is longer acting, and has a lower peak, than NPH insulin. Insulin degludec is a unique, ultra-long-acting basal insulin with reported duration of action up to 40 hours. It consists of soluble multi-hexamers, which

slowly dissociate after subcutaneous injection to provide a steady release of insulin monomers into the circulation (Fig. 2).

Though HbA1c data in children have not shown improvement with degludec,[2] its longer duration of action makes degludec attractive to pediatric endocrinologists for use in the adolescent population to reduce diabetic ketoacidosis (DKA) in this group of patients who are at risk of omitting insulin doses.

METHODS OF INSULIN DELIVERY

Multiple Daily Injections

For those patients and families reluctant to use wearable devices, insulin pens are the most convenient form of insulin delivery for multiple daily injections of insulin. The new smart pen (InPen™) is a reusable pen, which can be programmed for mealtime and correction bolus doses similar to the programming of an insulin pump. The smart pen has the capability of storing information, and its use may prevent dosing errors such as missed or duplicate doses, dose stacking, or erroneous calculations.

Pumps

Insulin pumps are programmable devices capable of delivering rapid-acting insulin doses as little as 0.025 units/hour for basal rates. The pump calculates bolus insulin doses based on formulas for mealtime (insulin to carbohydrate ratios) and correction doses (insulin sensitivity) set by the patient and the diabetes care team.

Early pump models delivered insulin only, and blood glucose levels had to be manually entered into the pump. The number of carbohydrates planned for the meal was also entered. The pump then calculated the dose needed to cover the carbohydrates, and calculated the correction dose needed if the blood glucose level was elevated. Today's pumps can

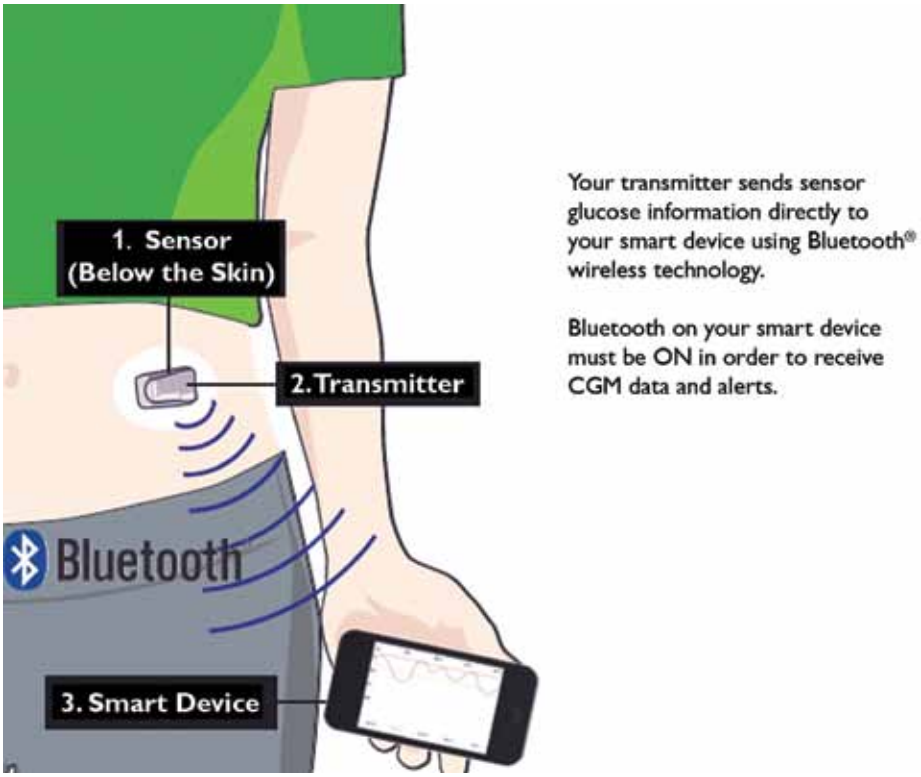

Fig. 3. Dexcom G5 Mobile CGM System Getting Started Guide

Comparison of Currently Available CGM Systems

Sensor	G5	G6	FreeStyle Libre	Enlite 2	Guardian 3	Eversense
Company	Dexcom	Dexcom	Abbott	Medtronic	Medtronic	Senseonics
Insertion	Applicator	Applicator	Applicator	Applicator	Applicator	Surgery
Sensor Life	7 days +	10 days	14 days	6 days	7 days	90 days
Calibration	2 / day	None	None	2 / day	2-4 / day	2 / day
Cost						
Receiver	Smartphone or Device	Smartphone or Device	Smartphone or Device	Receiver	Smartphone	
MARD	9%	9%	9.4%	13.6%	9.1-10.6%	8.5%
Alerts	Yes	Yes	No	Yes	Yes	Yes
Choose for...	None	Most T1D	T2D on insulin; T1D not wanting Dexcom; Other T2D?	None	670G only	T1D not wanting CGM visible 24/7

Fig. 4. Downloaded from https://aaronneinstein.com/2018/09/24/diabetes-technology-in-2018/

integrate blood glucose data directly from blood glucose monitors (meter or continuous glucose monitors). The use of insulin pumps has been shown to improve overall blood glucose levels while reducing hypoglycemia in pediatric patients.[3]

GLUCOSE MONITORING

Home blood glucose monitoring

Fingerstick monitoring of blood glucose has been available for 50 years. The accuracy of blood glucose readings should be within 20% of a laboratory glucose, the "gold standard." Today's devices are smaller than older models and some interact with insulin pumps. Nonetheless, the fingerstick remains burdensome and unpopular with patients and relies upon patient adherence. Data from most blood glucose monitors may be uploaded to share with the diabetes team in clinic or at home for dose adjustments between appointments.

Continuous Glucose Monitoring (CGM) utilizes sensors, which monitor glucose levels in the interstitial fluid. When glucose reacts with an enzyme on the sensor, an electrical current is generated, and higher interstitial glucose levels generate larger signals. The transmitter receives signals every few minutes and sends data to the receiver, allowing rapid recognition of blood glucoses changes and patterns (Fig. 3). Alarms can be set to alert patients and family members of impending hypo- or hyperglycemia. CGM devices include the glucose sensor worn by the patient, the transmitter, and the receiver. Patients and parents may receive data and alerts directly to their smart phones.

Accuracy of these systems is measured by mean absolute relative difference (MARD). This is the difference between CGM readings and blood glucose levels in clinical trials, and the lower the score, the greater the accuracy of the CGM. Sensors are now accurate enough to use for insulin dosing, but are less accurate at high or low extremes of blood glucose. Hypoglycemia and Hyperglycemia > 240 mg/dl should be confirmed by blood glucose measurements

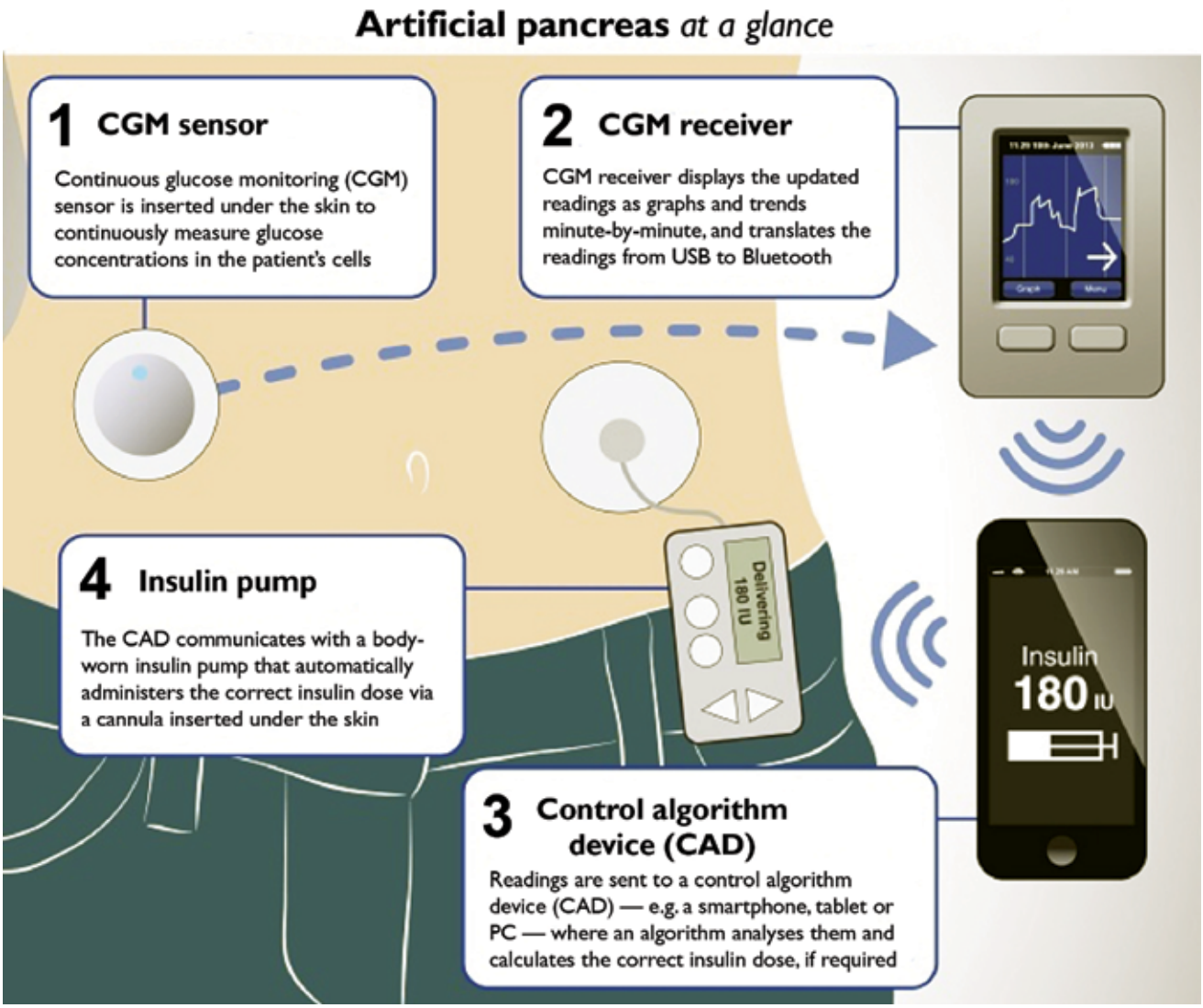

Fig. 5. Artificial Pancreas: What You Should Know
Tenderich A and Hoskins M. Diabetes Mine April 2019
https://www.healthline.com/diabetesmine/artificial-pancreas-what-you-should-know#1

prior to treatment.

There are several CGM systems on the market that variously provide information in real-time (Medtronic, Dexcom®), on intermittent scanning (Freestyle Libre™), and via an implantable device (Eversense™) (Fig. 4, preceding page). The latter sensor is implanted for 90 days and is not approved for use in children. Real-time devices are recommended for pediatric T1D because the alarms alert parents to nocturnal hypoglycemia. In the Children's Hospital of Philadelphia Diabetes Center, about 38% of T1D patients currently use CGM. CGM data may be uploaded in clinic or at home, and provide a comprehensive overview of blood glucose trends.

Closed loop systems are those in which the CGM communicates data directly to the pump, which then responds by adjusting insulin delivery (Fig. 5). If hypoglycemia is detected, the pump will suspend insulin delivery until the glucose level begins to rise. If the patient uses the pump in "auto mode," the pump will correct hyperglycemia by using algorithms to deliver microboluses of insulin every few minutes until hyperglycemia is corrected. Repeated episodes

of hyperglycemia over several days will result in the algorithm adjusting basal rates for that time period.

The Medtronic 670G closed loop system, which uses the Medtronic pump and Medtronic CGM, was introduced in 2017. Experience in pediatric patients thus far raises concerns that the algorithms may be too aggressive for younger children. Tandem has recently introduced a closed loop system called Control-IQ that uses its T-Slim pump and the Dexcom CGM®. It is approved for patients older than 14 years, with a black box warning against use in children under age 6 years.

The initial impressions of closed loop systems are:

- Diabetes-related work does not decrease, it changes;
- Patients lose some flexibility (no extended bolus, no temporary basal rates);
- The system chooses the correction dose and auto basal rates;
- Patients may change the carbohydrate ratio.
- The sensor is not always reliable.
- The algorithms are conservative for adults who desire tight blood glucose control, but may be too aggressive for young children.
- Some patients become frustrated, give up on auto mode, and use the pump only in manual mode.
- The system is effective in reducing hyperglycemia and hypoglycemia and may reduce fear of nocturnal hypoglycemia.

TROUBLESHOOTING

The most effective type of troubleshooting is prevention. According to the 2020 American Diabetes Association guidelines, the use of technology should be individualized based on a patient's needs, desires, skill level, and availability of devices.[4] The first step in the use of technology is to select the system that best fits the needs of the patient and family. With so many options available, families may be uncertain which monitoring or insulin delivery system to choose. The diabetes team assists families in reviewing options and making decisions in line with their needs and skill levels. The team also assesses whether the child wants to wear the technology around the clock, which is essential for insulin pump use. There are a number of software platforms available for uploading and reviewing data. As with all forms of technology, problems may arise, and patients must be trained on "troubleshooting."

CGM: Sensors do not always work properly. They may not pair with the receiver device or with a cell phone. Patients must then go back to fingerstick blood glucose checks until they obtain a new sensor.

Pumps: Patients using insulin pumps must be educated how to troubleshoot unexplained hyperglycemia. As there is no long-acting insulin in use, patients may deteriorate rapidly if not attended to. If an insulin pump patient is vomiting or showing signs of DKA (diabetic ketoacidosis) they should call 911 and go to the emergency room. Treatment of DKA is with IV insulin. Patients may resume use of the insulin pump when out of DKA, but they should troubleshoot along with the diabetes team.

Causes of unexplained hyperglycemia may be mechanical, behavioral, or physiologic/metabolic.

Steps to take include:

1. Check the insertion site: a new insertion site is needed in case of occlusion, a bent cannula, etc.
2. Check on insulin delivery: confirm the tubing is connected, there are no air pockets, etc.
3. Confirm that the proper insulin dose is being delivered: check the pump's history, evaluate carb dosing.
4. Verify that the insulin is stored properly and use a new vial if there is concern about spoilage.
5. Give insulin by injection if there is a mechanical pump problem; call the pump company for a replacement.

CONCLUSION

Diabetes technology, including insulin pumps, CGM systems, and closed loop systems, allows more precise insulin dosing. When used properly, real-time and intermittently scanned CGM systems are useful tools to increase the percent of time spent in target range and reduce the incidence of hypoglycemia. Bluetooth and smart phone connectivity allow for more rapid recognition of, and response to, blood glucose variability.

Hybrid systems have been referred to as the "artificial pancreas." In fact, they are not currently operating as automatically as a native pancreas, and there are some limitations to their use, but hybrid systems represent a significant step forward in the treatment of diabetes and the time spent in target range for diabetic patients.

Our ultimate goal is to improve the quality of life, reduce hypoglycemia, reduce diabetes–related hospitalizations, and lower the incidence of chronic complications for the nearly 200,000 Americans under the age of 20 years diagnosed with T1D.

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