TECHNOLOGICAL ADVANCES FOR TYPE 1 DIABETES MANAGEMENT

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MAY 1, 2022

No Disclosures

Technology for managing type 1 diabetes is rapidly advancing

Many are used off label in pediatric patients

OUTLINE

Diabetes mellitus overview

Traditional management of insulin dependent diabetes

Advances with insulin and glucagon

New technology with multiple daily insulin delivery devices

Continuous glucose monitors (CGM)

Automated insulin delivery algorithms

Integrated insulin pump and CGM

Other advancements

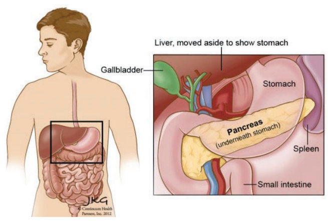
DIABETES MELLITUS

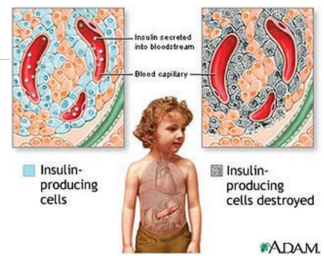
Group of diseases with pathology in glucose utilization due to islet cell destruction, insulin resistance, gain of function with specific genes leading dysregulated insulin release or scarring of the pancreas

Chronic diabetes conditions include:

- Type 1 diabetes
- Type 2 diabetes
- Cystic Fibrosis Related Diabetes
- Neonatal (monogenic) diabetes
- Gestational diabetes
- MODY (Maturity onset diabetes of the young)

TYPE 1 DIABETES





- Autoimmune disease
- T cells attack the insulin producing β-cells in the pancreas
- **Only treatment is insulin**

INCIDENCE RATE OF T1D

Incidence rate varies significantly by geographical region:

Sweden, Finland, Norway, United Kingdom, and Sardinia have the highest incidence
- Age-adjusted rate of > 20/100000 patient years

United States has an incidence rate:
- 17.8/100000 patient years in a predominantly Caucasian population

China and South America have the lowest incidence:
- < 1/100000 patient years

Rate of T1D diagnosis is increasing especially in children < 5 years

Annual incidence increasing globally by 2.3% per year

Simmons et al. WJD. 2015.

American Diabetes Association.

ADA Standards of Care 2021

Treatment with intensive insulin regimens, either via multiple daily injections or continuous subcutaneous insulin infusion

Self-monitor glucose levels up to 6–10 times/day by glucose meter or continuous glucose monitoring

Real-time continuous glucose monitoring in conjunction with insulin therapy is a useful tool to lower and/or maintain A1C levels and/or reduce hypoglycemia

Intermittently scanned continuous glucose monitoring in conjunction with insulin therapy can be useful to replace self-monitoring of blood glucose

Automated insulin delivery systems may be considered to improve glycemic control

A1C goals must be individualized and reassessed over time - A1C of <7% appropriate for many children (patient and provider dependent)

Continuous glucose monitoring metrics are recommended to be used in conjunction with A1C whenever possible

AGP Report

Name

MRN

GLUCOSE STATISTICS AND TARGETS

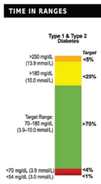
14 days
% Sensor Time

Glucose Ranges	Targets [% of Readings (Time/Day)]
Target Range 70–180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average Glucose
Glucose Management Indicator (GMI)
Glucose Variability
Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES



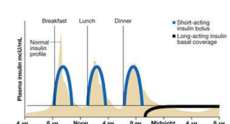
TRADITIONAL MANAGEMENT

Utilization of capillary blood glucose testing

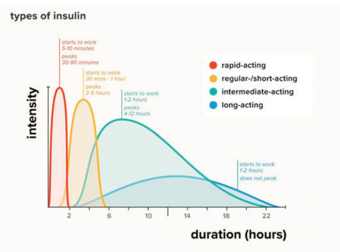
Multiple daily insulin injections with short and long-acting insulin

Continuous subcutaneous insulin infusion with use of short acting insulin only

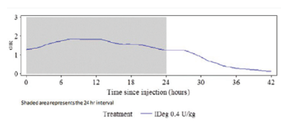
Manual corrections of high blood glucose levels



ADVANCES WITH INSULIN



Ultra-long-acting insulin – degludec lasts in system for 42 hours



Inhaled insulin (peaks at 12 minutes with insulin action time of 1.5-2 hours); not approved for under 18 years of age

ULTRARAPID ACTING INSULIN

Faster aspart - Fiasp is FDA approved for adults and children with diabetes	Ultrarapid lispro – URLi (Lyumjev) was FDA approved in 2020	BioChaperone lispro is currently in Phase 3 studies
• Uses nicotinamide as an excipient and l-arginine to increase stability • Overall rates of hypoglycemia and severe hypoglycemia have been reported to be similar between aspart and faster aspart	• Uses treprostinil to promote vasodilation and citrate as an excipient • A trial of URLi in patients with T1D showed decreased postprandial glycemic excursions at 1 and 2 hours compared with lispro	• uses BC222, an oligosaccharide modified with natural molecules and citrate as an excipient In a head-to-head study • BioChaperone lispro had slightly faster on-off kinetics than insulin lispro and may more closely mimic normal postprandial insulin secretion

Endocrinol Metab Clin North Am. 2020 Dec

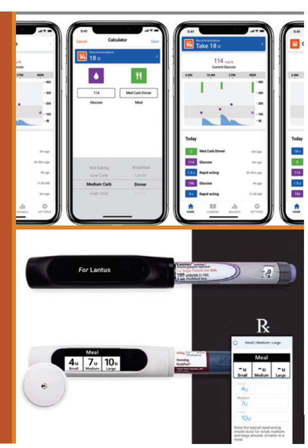
GLUCAGON

- POWDER + DILUENT (TRADITIONAL FORM)
- INHALED
- PREMIXED IN 2 DOSES (0.5 MG AND 1 MG)
- STABLE LIQUID FORMULATION (DASIGLUCAGON)

SMART INSULIN PENS

Use of pens with refillable insulin cartridges connected to smart phone app

- Reusable insulin pen that uses Bluetooth technology to send dose information to a mobile app
- Can incorporate integrated continuous glucose monitor data to automatically calculate and adjust insulin dosing



HISTORY OF GLUCOSE MONITORING

1908 - commercialization of urine glucose testing by heating copper reagent in urine

1945 – development of Clinitest (featured modified copper reagent tablet)

1965 – Dextrostix was developed; first blood glucose test strip using glucose oxidase

1980 - Dextrometer was launched; used the Dextrostix along with a digital display – more availability of self-monitoring of blood glucose

1980s, 1990s, and early 2000s – self monitoring technology continued to improve

1999 – first professional CGM was FDA approved

2004 - Medtronic introduced the Guardian REAL-Time CGM system

2006 - Dexcom introduced its first real-time CGM

2008 - FreeStyle Navigator by Abbott was released in the United States

2016 - Abbott introduced the FreeStyle Libre Pro

AUTOMATED INSULIN DELIVERY (AID)

AKA artificial pancreas (AP)

first clinical experiments of closed-loop AID in 1974 with IV dextrose to simulate food, IV sampling of blood glucose and IV insulin infusion

Main challenges:

Advancement of technology from proof-of-concept experiments in a clinical environment to daily use under free-living conditions

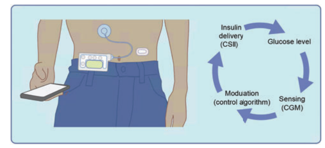
Developing hardware and control technologies to collect data, make decisions based on the data and manage insulin administration to maintain euglycemia

Three different types of algorithms

Proportional-integral-derivative (PID) control

Model predictive control (MPC)

Fuzzy-logic knowledge-based systems



Boughton and Hovorka (2021) Diabetologia.

PROPORTIONAL-INTEGRAL-DERIVATIVE CONTROL

PID Control

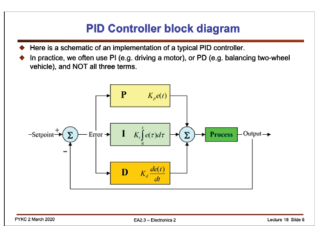
Used in various industries since the 1940s

Computes control action based on the difference between reference blood glucose and measured blood glucose

The difference or "error" is processed in three different ways

- proportional term considers the current value of the error
- integral term considers the sum of the errors over a past time window
- derivative term considers the rate of change in the last two errors

The proportional and derivative actions are similar to pancreas reaction to increase in blood glucose



MODEL PREDICTIVE CONTROL

Most of the AID systems use this modified version of this algorithm

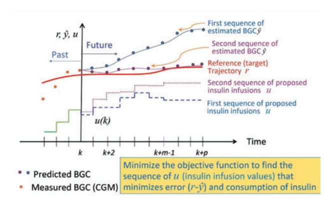
Uses a model of glucose and insulin dynamics to predict how the blood glucose will vary in the future in response to hypothetical set of future insulin infusions

Have four key elements:

- dynamic model of glucose and insulin dynamics for predicting future blood glucose values
- "objective function" that includes the sum of future errors between future blood glucose reference trajectories and blood glucose estimated by the model and the sum of the future insulin consumptions
- optimization algorithm to minimize the objective function defined
- constraints on the values and rates of change of BGC and insulin

Uses current and recent past values of sensor glucose readings and insulin infusion doses

Utilizes information captured from wearable devices such as heart rate, energy expenditure, and galvanic skin response to enhance the blood glucose prediction accuracy during periods of physical activity



FUZZY-LOGIC KNOWLEDGE-BASED SYSTEMS

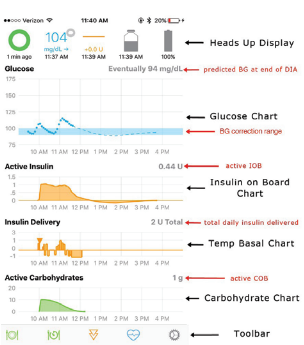
Knowledge-based systems capture the expertise of a care provider and the specific characteristics of an individual with type 1 diabetes in the form of “if-then” rules

Inferences are made by executing these rules, and insulin infusion suggestions are made based on the current state of the person

Fuzzy-logic is used to accommodate the day-to-day variations in unmeasured disturbances such as spontaneous physical activity and the occurrence of stressful events

Disadvantage of this approach is the high cost of maintenance of the system and the level of effort needed for modification to each patient

INTEGRATED DATA



BUILD IT YOURSELF SYSTEMS

The “build-it-yourself” systems consists of a combination of FDA-approved products (the pump and CGM) and a non-approved app which serves as the controller/algorithm

- Designed and built by people in the diabetes community who were looking for a better system than those that are commercially available
- Free apps - built by following a series of instructions that are available online
- Do not undergo regulatory overview and approval

BENEFITS AND CHALLENGES

- Increased time in target glucose range by 9.6 %
- Reduced time in hypoglycemia by 1.5 % (approximately 20 min/day) compared with control treatment
- Reduction of HbA1c by 0.3–0.4%
- Reduced anxiety
- Improved sleep and confidence from improved overnight glucose control
- Less restrictive eating habits
- “Time off” from the demands of diabetes management

- Technical issues
- Alarm intrusiveness
- Equipment burden

DUAL-HORMONE CLOSED-LOOP SYSTEMS

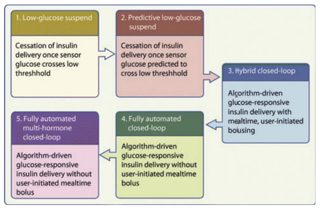
Addition of glucagon to a closed-loop system confers additional protection from hypoglycemia

May allow more aggressive insulin delivery to achieve improved glucose control

Potential benefits are countered by increased system complexity, requirement for two separate infusion systems

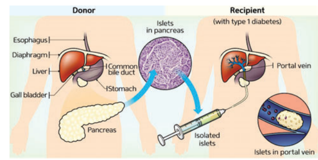
- Insulin and glucagon *use of dasiglucagon

There are currently no commercially available dual-hormone closed-loop systems, although several are in development.



Boughton, C.K., Hovorka, R. New closed-loop insulin systems. *Diabetologia*

ISLET CELL TRANSPLANT



First transplantation attempts, which began in the 1990s, succeeded only 8% of the time, which was attributed to the fact that anti-rejection drugs available at the time interfered with insulin's effectiveness

Clinical trial in 1999 conducted at the University of Alberta in Edmonton, Canada, brought new hope

- Using enhanced techniques to collect and prepare the extremely fragile donor islet cells, as well as using improved anti-rejection drugs
- Researchers achieved a 100% success rate with all patients in their trial were freed from the need for insulin for at least one month.
- Not as successful in later trials, and the number of islet cell transplantations has decreased in more recent years

The Collaborative Islet Transplant Registry reported in 2009 that 70% of adults with T1D were free of insulin injections at one year, 50% at two years, and 35% at three years.

There are currently 17 U.S. centers participating in islet cell research programs

FUTURE INNOVATIONS FOR DIABETES CARE

Immunotherapy to suppress ongoing β cell autoimmunity by restoring peripheral tolerance without affecting protective immunity, and preserving β cell function

Converting human stem cells into beta cells capable of producing insulin using small molecules in the laboratory

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