TECHNOLOGICAL ADVANCES FOR TYPE 1 DIABETES MANAGEMENT
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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

**ADA Standards of Care 2021**

- Treatment with intensive insulin regimens, either multiple daily injections or continuous subcutaneous insulin infusions
- Self-monitoring of blood glucose 4-10 times/day for blood glucose meter or continuous glucose monitoring
- Continuous subcutaneous insulin infusions in conjunction with insulin regimen with basal insulin
- Real-time continuous glucose monitoring in conjunction with insulin therapy
- Continuous glucose monitoring metrics are recommended to be used in conjunction with A1C

**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 – FDA approved for adults and children with diabetes
  - 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

- Ultrarapid lispro – FDA approved in 2020
  - 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

- BioChaperone lispro is currently in Phase 3 studies
  - 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

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**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 Clinistix (featured modified copper reagent tablet)
1965 – Dextrostix was developed; first blood glucose test strip using glucose oxidase

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)

Main challenges:
- Advancement of technology from proof-of-concept experiments 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

Three different types of algorithms:
- Proportional-integral-derivative (PID) control
- Model predictive control (MPC)
- Fuzzy-logic knowledge-based systems

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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

Main key elements:
- Dynamic model of glucose and insulin dynamics for predicting future blood glucose values
- Objective function – cost function that includes the sum of future errors between measured blood glucose and the model predicted glucose values, insulin consumption
- Optimizer algorithm to minimize the objective function defined

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Uses information captured from wearable devices (sleep, heart rate, physical activity) to enhance blood glucose prediction and insulin infusion dose
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 2.5% (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.

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