Innovations in Diabetes Care and Management
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Objectives

1. Briefly discuss the history of diabetes management over the past 100 years
2. Describe the impact of new technology and medical devices on the lives of People with Diabetes
3. Share the personal story of a Person with Diabetes and how they utilize the new hybrid insulin pump

We’ve come a LONG way, baby .........

The Problem

- 30.1 million Americans are affected by diabetes—this includes 23.1 million diagnosed and 7.2 million people who are unaware they have the disease. This computes to 23.8% of people are undiagnosed.
- One of the top 10 causes of death in the United States, diabetes has far-reaching implications for patients and their families and our health care system.
- According to the CDC, the number of Americans diagnosed with diabetes has more than tripled since 1980

Treating Diabetes

- Healthy eating and exercise can help prevent and manage type 2 diabetes.
- Medicines play a key role in helping reduce the risk of and treat the disease.
  - One medicine was found in studies to lower the risk by 31%.
  - In recent years, eight new classes of type 2 diabetes medicines have been approved by the Food and Drug Administration (FDA).
- 180 new medicines for type 1 and type 2 diabetes and diabetes-related conditions, such as chronic kidney failure due to diabetes and painful diabetic neuropathy, are currently in development by America's biopharmaceutical research companies.

Innovations in DM Care

- New Medications
  - Goal - provide each person with diabetes an individualized tailored therapy.

Non-insulin DM meds
- Sulfonylureas
- Biguanides
- Meglitinide derivatives
- Alpha-glucosidase inhibitors
- Thiazolidinediones (TZDs)
- DPP4 inhibitors
- SGLT2 Inhibitors
- Bile Acid Sequestrants
- Dopamine agonists
Non-insulin injectables

GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Formulation</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trulicity</td>
<td>degludec</td>
<td>6.25 mg weekly; third dose may increase to 5 mg once weekly</td>
</tr>
<tr>
<td>Rybelsys</td>
<td>weekly LIR</td>
<td>1 mg once weekly</td>
</tr>
<tr>
<td>Toujeo</td>
<td>inhaled</td>
<td>50 mg once weekly; initially increased to 100 mg once weekly</td>
</tr>
<tr>
<td>Ozenisa</td>
<td>degludec</td>
<td>2.5 mg at bedtime for 1 week; 5.0 mg at bedtime may increase to 10 mg daily</td>
</tr>
<tr>
<td>Affinity</td>
<td>inhalant</td>
<td>2 mg at bedtime for 2 weeks; then 5 mg daily</td>
</tr>
<tr>
<td>Setpoint</td>
<td>semaglutide</td>
<td>1 mg in 60 minutes prior to meal, may increase to 2.0 mg daily</td>
</tr>
</tbody>
</table>

Benefits beyond BG reduction:
- ↓ CV Mortality
- Low risk of hypoglycemia
- Promote fullness and weight loss (1-5 kg)
- ↓ post-meal BG
- ↓ HbA1C (1-2 mmol/L)
- ↓ Tls (12-40 mg/dL)
- Beta-cell preservation?
New Insulin Products

- Basal (long-acting)
  - Tresiba® (insulin degludec)
  - Toujeo® (insulin glargine U-300)
  - BasalAct® (insulin glargine U-500)

- Bial (rapid; mealtime)
  - Humalog® U-100 (insulin aspart U-100)

- Other
  - Humulin R® U-500 Kwikpen® and syringe

- Combination Products
  - Solixtra® (insulin glargine/insulatard®)
  - Lant��® (insulin glargine/Zilprozide)
  - Rosez® (insulin degludec/insulin aspart)

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Tresiba® (insulin degludec)

- "Ultra-long" 42+ hour duration of action
- Available in 100 units/mL or 200 units/mL
- No PK difference between U-100 and U-200

- Versus Levemir® or Lantus®:
  - Similar ASC reduction
  - Lower within-day and within-subject variability
  - Lower hypoglycemia and nocturnal hypoglycemia

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Toujeo® (insulin glargine U-300)

- 30+ hour duration of action
- Versus Lantus®:
  - Similar ASC reduction
  - Lower within-day and within-subject variability
  - Lower hypoglycemia and nocturnal hypoglycemia
  - Slightly less weight gain (0.2-0.7 kg)
Basaglar® (insulin glargine U-100)

- First "follow-on" insulin
- Lantus® patient recently expired
- Biologic drugs: different FDA regulations, no "generics"
- Basaglar®: "highly similar" to Lantus®
- Compared with Lantus®:
  - A equivalent PLM/PK
  - Non-inferior efficacy and safety
  - Clinical trials too small/short to identify rare safety events

U-500 Insulin Syringe

U-500 insulin syringe also now available!

Humulin-R® U-500 Kwikpen®

- U-500 insulin now available in a pen!
- Same drug, less risk of confusion
- Pen contains 2000 units of insulin
- Dosage 5 unit increments up to max 300 units per injection
- Crucial to ensure patient understanding of dose prior to switching

Combination Products

- Soliqua® (insulin glargine and lixisenatide):
  - Dosed once daily without regard to food
  - Each dosing increment contains 3.3 units of glargine and 0.15 mg of lixisenatide
  - Recommended starting doses:
    - Taking 10 units basal insulin and 12 mg lixisenatide: 15 units glargine / 3 mg lixisenatide
    - Taking 36 units basal insulin: 30 units / 10 mg
  - Max dose: 60 units / 20 mg
Combination Products

- Xultophy® (insulin degludec and lixisludine)
  - Dosed once daily, regardless of food
  - Each dosing increment contains 1 unit of degludec and 0.008 mg of lixisludine
  - Recommended starting dose: 16 units degludec / 0.292 mg lixisludine
  - Max dose: 72 units / 3.8 mg

Summary Table 1 – New Insulin Products

<table>
<thead>
<tr>
<th>Drug</th>
<th>Insulin Type</th>
<th>Dose</th>
<th>Adverse Effects</th>
<th>Available in US</th>
<th>Availability in Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine U40</td>
<td>U-40</td>
<td>0.6 units/day</td>
<td>Hypoglycemia, weight gain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Glargine U30</td>
<td>U-30</td>
<td>0.4 units/day</td>
<td>Hypoglycemia, weight gain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lispro U50</td>
<td>U-50</td>
<td>0.8 units/day</td>
<td>Hypoglycemia, weight gain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lispro U40</td>
<td>U-40</td>
<td>0.6 units/day</td>
<td>Hypoglycemia, weight gain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lispro U30</td>
<td>U-30</td>
<td>0.4 units/day</td>
<td>Hypoglycemia, weight gain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Opportunities to Improve Insulin

- Faster onset, Aflrezza
- Longer duration, Toujeo, Tresiba
- Less variable PK, Toujeo, Tresiba
- More concentrated, Toujeo, Tresiba, Nanoflex, O-300

To learn more -

www.Drugs.com
Oral insulin

- Novo Nordisk was investigating a tablet formulation of insulin that is swallowed once daily and slowly absorbed into blood stream. Study to compare to injected basal glargine resulted in equally improved A1c. This was only an 8 week study on 50 people.
- Results were reported at ADA but development has been discontinued due to excessive cost.

Glucagon

- Nasal powder - Eli Lilly
- Patch - Zosano Pharma
- Pen - Xeris Pharmaceuticals

Treating Hypoglycemia

- Pills for prevention - looking for agents that could be taken in pill form to prevent hypos
- Micro-doses - currently being developed as a pen that person could carry with them at all times to treat mild hypoglycemia
- Dual-hormone artificial pancreas - used in a pump type delivery system. Major problem is developing glucagon that is stable in liquid form and effective for long term use.

Innovations in DM Management

- New Technologies
  - Intarcia Mini-Pump for GLP1 - stalled
  - Insulin Delivery Systems
    - V-Go Patch pump
    - Medtronic 770G - Hybrid Closed-Loop System
  - Continuous Glucose Monitoring Systems
    - Dexcom
    - Abbott FreeStyle Libre - personal
    - "wand style" intermittent glucose monitor
V-Go patch pump

- The V-Go is a simple-to-use, once-daily, disposable insulin delivery device. This spring-driven patch pump is worn on the skin to provide a preset basal rate and on-demand bolus dosing. Valeritas designed the device to be convenient and easy to use for people with Type 2 diabetes who use multiple daily injections.

OmniPod • tubeless insulin pump

- 2018: projected launch of new DASH platform which sends pump info to Glooko w/o patient intervention. Will lose phone connectivity.

Advantages of Continuous Subcutaneous Insulin Infusion (CSII) vs Multiple Dose Insulin Injections

- Programmable insulin delivery allows closer match with physiologic needs
- Uses only rapid-acting insulin, minimizing peaks and absorption-related variability
- Uses one injection site for up to 72 hr, thus reducing variations in absorption and treatment-related burden from multiple injections
- Reduction in glycemic variability and improved glycemic control
- Decreased risk of severe hypoglycemia and need for emergent medical attention
- Reduction in need for hospitalization and cost of care
- Improved quality of life and treatment satisfaction

Insulin Pump Issues

- Mechanical malfunction
- Insertion site issues such as inflammation or, rarely, skin infections
- Interruption of insulin supply due to kinking or blockage of the infusion set can lead to the rapid development of extreme hyperglycemia, especially in type 1 diabetes
- These factors may sometimes necessitate discontinuation of pump use and temporary reversion to insulin injections.
- Safeguards such as alarms that warn of delivery problems or low amounts of insulin in the reservoir are now standard features in insulin pumps.
- Psychological issues of being connected to a machine
Medtronic Paradigm Insulin Pump

- **SmartGuard Technology**: Lowers insulin based on glucose trends. Only the Medtronic system has SmartGuard technology, which takes action if sensor glucose values go below a preset level. If the patient doesn’t respond to alarms, SmartGuard technology can pause insulin delivery for up to two hours - giving time to recover.

- **Bolus Wizard® Calculator**: This feature automatically calculates and recommends precise bolus doses to help avoid insulin stacking if boluses are accidentally set too close together.

- **Predictive Alerts**: The pump alerts wearer up to 30 minutes ahead if they’re trending high or low, so they can act sooner to keep glucose levels in proper range.

- **Built-in CGM**: The sensor wirelessly sends glucose information to the pump every five minutes, so wearer can track how they are doing, spot trends and make adjustments.

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Medtronic 630G

- **SmartGuard Technology**: The pump alerts wearer when sensor glucose values go below a preset level, giving up to two hours of insulin delivery pausing if the patient doesn’t respond to alarms.

- **Bolus Wizard® Calculator**: Automatically calculates and recommends precise bolus doses to prevent insulin stacking.

- **Predictive Alerts**: Alerts wearer up to 30 minutes ahead if glucose values are trending high or low, allowing for early intervention.

- **Built-in CGM**: Sends glucose information wirelessly to the pump every five minutes, enabling wearer to track trends and make adjustments.
Closed Loop Insulin Delivery
- Recently approved by FDA.
- Consists of an insulin pump, a sensor and a blood glucose monitor.
- The sensor communicates with the pump, allowing it to adjust insulin administration based on glucose patterns.
- The sensor is calibrated two times a day with a separate blood glucose monitor.
- Utilizing glucose information, the pump changes or even "suspends" insulin delivery if the glucose levels fall below a preset target.
- Alerts wearer to drops in glucose, allowing the wearer to verify the glucose value with a finger stick and to consume a snack to correct the low glucose if needed.
- Significantly decreases hypoglycemic events, especially during the night.
- Alerts the wearer to rapid rises in glucose while it readjusts the insulin rate to correct the elevated glucose.
- Provides newfound stability of blood glucose.
- Essential elimination of hypoglycemic events and reduces glucose excursions.

Artificial Intelligence in DM Management
- Dr. Moshi Vardi – professor at Rice University and expert on AI.
- Machines can now rely on “learned” intuition.
- The paradox is in answer to the idea of computers, automation and AI replacing humans.
- Polanyi’s Paradox
- The paradox is described as “We can know more than we can tell, i.e. many of the tasks we perform rely on tacit, intuitive knowledge that is difficult to codify and automate.”
- Huge impact on Diabetes Management.
Medtronic 670G

- The Suspend before low option avoids lows and rebound highs proactively by automatically stopping insulin 30 minutes before reaching pre-selected low limits. The pump then automatically restarts insulin when glucose levels recover, without alerts.
- The Auto Mode option automatically adjusts basal insulin delivery every 5 minutes based on glucose levels to maintain target range, 24 hrs a day.
- Guardian Sensor 3 continuous glucose monitoring sensor. Can wear up to 7 days. The FIRST and ONLY continuous glucose monitoring sensor FDA approved on which to base insulin dosing.
- Exclusive CONTOUR®NEXT LINK 2.4 meter provides easy and accurate CGM calibration, insulin dosing and remote bolusing.

www.medtronicdiabetes.com

Tandem t:slimx2

- Integrated with Dexcom G5 sensor
- Allows for remote software updates. Pts will be able to download updates w/o buying a new pump.

Dexcom G5 CGMS

- The first FDA-approved CGM System to make treatment decisions without fingersticks.
- Reads glucose every five minutes - and where it's heading - with just a glance at a compatible smart device or Dexcom Receiver.
- At least 2 fingersticks required for calibration, or if symptoms or expectations do not match readings.
- NOTE: Interacts with medications containing acetaminophen.

Dexcom G5

- The first FDA-approved CGM System to make treatment decisions without fingersticks.
Sensor Data

Abbott FreeStyle Libre Pro
Continuous Glucose Monitoring System

FreeStyle Libre - FLASH Personal CGMS
Approved by FDA to be used for treatment without calibration finger sticks

+Stays on the body for up to 10 days
+No fingerstick calibration required
+Automatically measures glucose every minute

Libre graphs
Gene transfer

- US Patent granted to Ralph A DeFronzo, MD and Bruno Doiron, PhD of UT Health San Antonio
- Plan is to alter other cells of the pancreas so that they secrete insulin in response to glucose.
- Utilizing gene transfer, a virus is used as a vector or carrier to introduce selected genes into the pancreas. These genes become incorporated and cause digestive enzymes and other cell types to make insulin.
- Gene transfer using a viral vector has been approved nearly 50 times by the FDA to treat other diseases.
- Replication of all beta cells (T1DM) is not needed. Only 20% of cell restoration is sufficient to cure T1DM.

New Technologies

- Websites
  - AmericanDiabetesAssociation.org
  - DiabetesEducator.org
  - NIDDK.nih.gov
  - dhs.texas.gov/TDCtoolkit.asp
  - CDC.gov/diabetes/HIIEP
  - DiabetesResourceGuide.com
  - Sponsored by Humana and the American Diabetes Association