Updates and Innovations in Diabetes Technology

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Disclosures

Research Support:
Novo Nordisk
Helmsley Charitable Trust

Consultant- Dexcom

Advisory Board- Diasend
**History Of DM And Technology**

**Urine flavor wheel**

**Urine glucose kit, Lilly, 1930**

**Sugar Acetone Determination, 1970s**

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**Thomas Willis (1621-1675):**

"The urine was wonderfully sweet as if it were imbued with honey or sugar"

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**Early Insulin Pen**

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**"The Guillotine"**

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**Dextrostix Glucose Meter**

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**Early glucose monitor testing kits**
Fast Forward 30 Years...
Evolution of Diabetes and Technology

- Insulin Pump
- Continuous Glucose Monitoring (CGM)
- Integration of Insulin pump and CGM
- Artificial Pancreas
Insulin Pumps

- Computerized medical devices that provide continuous subcutaneous infusion of rapid acting insulin

- Several components:
  - Pump
  - Reservoir
  - Infusion set with cannula

- The ultimate basal/bolus regimen
  - Flexible basal rates
  - Variable carbohydrate to insulin ratio settings
  - Advanced features: programmable bolus duration
  - Variable basal rates settings for special situations (physical activity, stress, illnesses, NPO for surgery)
How Does Insulin Pump Deliver Insulin?

Cut-section view of skin

- Insulin pen injector
- Insulin jet injector
- External insulin pump
Use of Insulin Pump in USA

- T1 DM: 20% to 30%
- T2 DM ~ 2%
- US FDA data: between 375,000 and 515,000 individuals (2012)
Pump Therapy Improves Hba1c

Litton J, et al J pediatr 2002; 141-495
### CSII vs. MDI – HbA1c

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Mean Between-Group Difference in HbA1c Change From Baseline, %</th>
<th>Mean Difference (95% CI)</th>
<th>CSII, n</th>
<th>MDI, n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children/adolescents with T1DM</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Doyle et al, 2004 (32)</td>
<td>-0.80 (-1.89 to 0.29)</td>
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<tr>
<td>Schiaffini et al, 2007 (35)</td>
<td>-0.60 (-1.43 to 0.23)</td>
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<tr>
<td>Cohen et al, 2003 (31)</td>
<td>-0.52 (-1.67 to 0.63)</td>
<td>15</td>
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<tr>
<td>Nuboer et al, 2008 (33)</td>
<td>-0.16 (-0.68 to 0.36)</td>
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<td>Opipari-Arrigan et al, 2007 (34)</td>
<td>-0.13 (-1.74 to 1.48)</td>
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<tr>
<td>Skogsberg et al, 2008 (36)</td>
<td>0.00 (-1.25 to 1.25)</td>
<td>34</td>
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<tr>
<td>Weintrob et al, 2003 (37)</td>
<td>0.26 (-0.32 to 0.84)</td>
<td>11</td>
<td>12</td>
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</tr>
<tr>
<td><strong>Subtotal (I² = 0.0%; P = 0.561)</strong></td>
<td>-0.17 (-0.47 to 0.14)</td>
<td>–</td>
<td>–</td>
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<tr>
<td><strong>Adults with T1DM</strong></td>
<td></td>
<td></td>
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<tr>
<td>DeVries et al, 2002 (40)</td>
<td>-0.84 (-1.31 to -0.37)</td>
<td>39</td>
<td>40</td>
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<tr>
<td>Thomas et al, 2007 (44)</td>
<td>-0.10 (-2.12 to 1.92)</td>
<td>7</td>
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<td>Bolli et al, 2009 (39)</td>
<td>-0.10 (-0.52 to 0.32)</td>
<td>24</td>
<td>26</td>
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<tr>
<td>Tsui et al, 2001 (45)</td>
<td>0.25 (-0.42 to 0.92)</td>
<td>13</td>
<td>14</td>
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<tr>
<td><strong>Subtotal (I² = 64.5%; P = 0.038)</strong></td>
<td>-0.30 (-0.58 to -0.02)</td>
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<tr>
<td><strong>Subtotal, excluding DeVries et al (I² = 0.0%; P = 0.684)</strong></td>
<td>-0.01 (-0.35 to 0.34)</td>
<td>–</td>
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<tr>
<td><strong>Adults with T2DM</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Derosa et al, 2009 (47)</td>
<td>-0.50 (-1.57 to 0.57)</td>
<td>32</td>
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<tr>
<td>Wainstein et al, 2005 (50)</td>
<td>-0.50 (-1.57 to 0.57)</td>
<td>20</td>
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<tr>
<td>Raskin et al, 2003 (49)</td>
<td>-0.16 (-0.51 to 0.19)</td>
<td>66</td>
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<td>Herman et al, 2005 (48)</td>
<td>-0.10 (-0.52 to 0.32)</td>
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<tr>
<td><strong>Subtotal (I² = 0.0%; P = 0.840)</strong></td>
<td>-0.18 (-0.43 to 0.08)</td>
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</table>
## Insulin Pump Therapy

### Hba1c Improvement Over 3 Years

<table>
<thead>
<tr>
<th></th>
<th>Year</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>BMI</td>
<td>26.25±5.39</td>
<td>26.45±5.18</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.38±15.36</td>
<td>73.96±15.13</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.6±1.8</td>
<td>7.2±0.9</td>
</tr>
<tr>
<td>Insulin (IU)</td>
<td>27.7±13.8</td>
<td>28.6±13.4</td>
</tr>
<tr>
<td>Basal</td>
<td>17.1±7.4</td>
<td>16.9±9.1</td>
</tr>
<tr>
<td>Bolus</td>
<td>1.71±0.6</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>Basal to bolus ratio</td>
<td>1.71±0.6</td>
<td>1.8±0.8</td>
</tr>
<tr>
<td>Hypoglycemic episodes</td>
<td>26.6±28.2</td>
<td>21.6±24.2</td>
</tr>
<tr>
<td>(events/month)</td>
<td>0.05±0.2</td>
<td>0.05±0.2</td>
</tr>
<tr>
<td>Infection by the pump</td>
<td>194.1±32.9</td>
<td>190±31.3</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>48.6±17.4</td>
<td>48.6±17.2</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>122.4±33.8</td>
<td>119±31.6</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>114.9±66.3</td>
<td>111.6±59.3</td>
</tr>
</tbody>
</table>
Severe Hypoglycemia MDI vs CSII

T1D Exchange
Insulin Pump Use (2016)

Age (years)

- Overall: 64%
- <6: 63%
- 6-<13: 67%
- 13-<18: 63%
- 18-<26: 59%
- 26-<50: 66%
- 50-<65: 65%
- ≥65: 62%
Racial Disparities in Pump Use

- **<18 yrs**
  - White: 69%
  - Afr-Am: 35%
  - Hispanic: 49%

- **≥18 yrs**
  - White: 65%
  - Afr-Am: 38%
  - Hispanic: 48%
Lower HbA1c in Insulin Pump Users

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Injection</th>
<th>Insulin Pump</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;13</td>
<td>8.6%</td>
<td>8.2%</td>
</tr>
<tr>
<td>13-&lt;26</td>
<td>9.3%</td>
<td>8.6%</td>
</tr>
<tr>
<td>≥26</td>
<td>7.8%</td>
<td>7.6%</td>
</tr>
</tbody>
</table>
Lower HbA1c in Pump Users Across Races/Ethnicities

- **White**
  - Injections: 8.5%
  - Pump: 8.2%

- **African-Am**
  - Injections: 9.8%
  - Pump: 9.1%

- **Hispanic**
  - Injections: 9.3%
  - Pump: 8.4%
Why Isn’t Pump Therapy Sufficient To Achieve Hba1c Target?

It Needs CGM, The “Eye-opener”!

CGM = Continuous Glucose Monitoring
The Value Of Continuous Glucose Monitoring
Fewer highs = less complications

Fewer lows = less accidents, seizures, etc
Benefits of CGM

• Tracking and trending information to assess glycemic control

• Immediate feedback, with an opportunity to decrease glycemic excursions

• Adjustable high and low alerts

• Peace of mind from fear of low blood sugars

• Contributes to behavior modifications
How Do Sensors Work?

Glucose + O₂ → H₂O₂ + Gluconic Acid

H₂O₂ → 2H⁺ + O₂ + 2 e⁻

Oxygen utilized in reaction
Peroxide produced in reaction

CGM Clinical Indications

- **Hypoglycemia** and hypoglycemia unawareness
  - Identifies causes of hypoglycemia

- **Gastroparesis**
  - Helps with timing of insulin delivery

- **Glycemic Variability** - fluctuation of glucose values leads to oxidative stress, increasing cell damage and risk for micro- and macrovascular complications

- **Preconception**
  - Tight glucose control critical before conception
  - Increased risk of nocturnal hypoglycemia
  - Tight post prandial control challenges
Insulin Pump Integration With CGM

2008

2009

2013

2014

2015
CGM Use in the T1D Exchange Clinic Registry (2016)

- Overall: 17%
- <6: 32%
- 6-<13: 17%
- 13-<18: 10%
- 18-<26: 12%
- 26-<50: 27%
- 50-<65: 27%
- ≥ 65: 18%
Lower HbA1c in CGM Users

- **<13 years old**: Non CGM Users: 8.5%, CGM Users: 7.8%
- **13-<26 years old**: Non CGM Users: 9.0%, CGM Users: 8.2%
- **≥26 years old**: Non CGM Users: 7.8%, CGM Users: 7.4%

Source: Northwestern University Feinberg School of Medicine
CGM Use Is Increasing But Still Low

Enrolled 2010-2012 (7% use CGM overall)

Current 2015 (17% use CGM overall)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;6</th>
<th>6-&lt;13</th>
<th>13-&lt;18</th>
<th>18-&lt;26</th>
<th>26-&lt;50</th>
<th>50-&lt;65</th>
<th>≥ 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>4%</td>
<td>4%</td>
<td>3%</td>
<td>4%</td>
<td>15%</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>6-&lt;13</td>
<td>17%</td>
<td>4%</td>
<td>10%</td>
<td>12%</td>
<td>27%</td>
<td>27%</td>
<td>18%</td>
</tr>
</tbody>
</table>

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FEINBERG SCHOOL OF MEDICINE
T1D Exchange
Barriers to CGM Use

- Technical issues
  - Accuracy and reliability
  - Alarms and alerts
  - Insertion problems/“one more thing to carry”

- Financial issues

- Healthcare professionals’ attitudes

Pickup JC et al, Diabetes Care 2015
## Personal CGM Devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Calibration</th>
<th>Approval</th>
<th>Interference</th>
<th>Duration</th>
<th>MARD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic Enlite®†</td>
<td>Q12 hours (best with 3-4/Day)</td>
<td>&gt;16 yo</td>
<td>Acetaminophen</td>
<td>6 days</td>
<td>13.6%</td>
</tr>
<tr>
<td>Dexcom G4® Platinum</td>
<td>Q 12 hours</td>
<td>&gt;2 yo</td>
<td>Acetaminophen</td>
<td>7 days</td>
<td>10.8%</td>
</tr>
<tr>
<td>Dexcom G5™ Mobile</td>
<td>Q 12 hours</td>
<td>&gt;2 yo</td>
<td>Acetaminophen</td>
<td>7 days</td>
<td>9%</td>
</tr>
</tbody>
</table>

† Integrated in Medtronic 530 G pump

*MARD, mean absolute relative difference
CGM And Insulin Dosing: T1D Exchange

Adult CGM Users Questionnaire

- **26%** always verify CGM glucose with BGM before meal bolus

- **41%** verify CGM glucose with BGM before meal bolus ≤ 50% of the time

- No difference in severe hypoglycemia frequency (3 months)
**REPLACE-BG Study**

- **Objective**: To determine whether the routine use of CGM without BGM confirmation is as safe and effective as CGM used as an adjunct to BGM.

- **Primary Outcome**: Time in range 70-180 mg/dl, measured with CGM over the full 6 months of the study.

- **Safety Mitigations**:
  - Population restriction
  - Protocol stipulations

**www.ClinicalTrials.gov**
T1D Exchange Clinic Network, 2015
Participants who successfully complete the run-in phase will be randomly assigned to one of two treatment groups in a 2:1 ratio
- CGM Only group
- CGM+BGM group
Usefulness of CGM Downloads

- Uncover undiagnosed hypo and hyperglycemia
- Recognize patterns and trends
- Look at specific days of the week
- Recognize effect of meals, exercise on glucose
- Make therapeutic interventions
Daily Trends

24 Hour period
Suspending pump and Too Many Manual Boluses

Saturday 6/4

Breakfast
Lunch
Dinner
Effects of exercise on increased insulin sensitivity
Overtime Improvement

64 yo woman T1DM for 30 yrs on CSII.
Large consumption of rice at lunch, protein at dinner.
Overtime Improvement - 1 month later
Detailed Information
Meals, Exercise, Temporary Basal

Tuesday 12/8/2015

Data Sources: MiniMed 530G - 751

Medtronic

Glucose (mg/dL)

Carbs (g)

Insulin (U/hr)

12 AM 2 AM 4 AM 8 AM 10 AM 12 PM 2 PM 4 PM 6 PM 8 PM 10 PM 12 AM

1 2 3 4 5 6 7 8 9 10 11 12
Detailed Information
Meals, Exercise, Temporary Basal

Saturday 3/19/2016

Data Sources: MiniMed 530G - 751
DEXCOM G5 Clarity
The “Closed Loop”

- A system designed to respond to glucose changes by mimicking the actions of a normal-functioning pancreas without interaction from the patient (the artificial pancreas)

- The prototype system consists of three elements:
  - Insulin delivery (insulin pump)
  - CGM
  - Algorithm that regulates the correct amount of insulin delivered at the appropriate time
The Artificial Pancreas
The Sensor Augmented Pump

**The Bionic Pancreas - NEJM 2014**

A Mean Glucose Levels in Adults

- **Bionic pancreas**
- **Control**

<table>
<thead>
<tr>
<th>Glucose (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>350</td>
</tr>
<tr>
<td>300</td>
</tr>
<tr>
<td>250</td>
</tr>
<tr>
<td>200</td>
</tr>
<tr>
<td>150</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>50</td>
</tr>
</tbody>
</table>

**Time**

- 6 p.m.
- Midnight
- 6 a.m.
- Noon
- 6 p.m.
- Midnight
- 6 a.m.
- Noon
- 6 p.m.
- Midnight
- 6 a.m.
- Noon
- 6 p.m.
- Midnight
- 6 a.m.
- Noon
- 6 p.m.

B Mean Glucose Levels in Adolescents

- **Bionic pancreas**
- **Control**

<table>
<thead>
<tr>
<th>Glucose (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>350</td>
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<td>300</td>
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<td>250</td>
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<td>200</td>
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<tr>
<td>150</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>50</td>
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</tbody>
</table>

**Time**

- 3 p.m.
- 9 p.m.
- 3 a.m.
- 9 a.m.
- 3 p.m.
- 9 p.m.
- 3 a.m.
- 9 a.m.
- 3 p.m.
- 9 p.m.
- 3 a.m.
- 9 a.m.
- 3 p.m.

Aspire At Home Study

Reduction of Nocturnal Hypoglycemia

**Baseline A1C <7%**

<table>
<thead>
<tr>
<th>Category</th>
<th>TS</th>
<th>Control</th>
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<tbody>
<tr>
<td>Decreased</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Stable</td>
<td>29</td>
<td>38</td>
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<tr>
<td>Increased</td>
<td>10</td>
<td>8</td>
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</table>

**Baseline A1C 7-8%**

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<tbody>
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<td>Stable</td>
<td>31</td>
<td>33</td>
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<tr>
<td>Increased</td>
<td>16</td>
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**Baseline A1C >8%**

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<td>5</td>
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<tr>
<td>Stable</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Increased</td>
<td>0</td>
<td>4</td>
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</table>
Medtronic Closed Loop - Artificial Pancreas Timeline

2006: The Foundation
- World's first integrated insulin pump and CGM system. Shows real-time CGM information on the pump and delivers alerts/alarms based on sensor values

2009-2013: Taking Action
- Automatically stops insulin delivery when sensor reaches low threshold

2015: Predicting Low
- Stops insulin before the sensor reaches low threshold and resumes when sensor glucose levels recover

MiniMed Veo (OUS)*
- MiniMed 530G (US)

MiniMed 640G (OUS)*

Under Investigation: Hybrid Closed Loop
- Automatic insulin delivery, patients need only to calibrate the sensor and enter mealtime carbs

GOAL
- Fully automatic insulin delivery with minimal patient interaction required

* Not approved for use nor commercially available in the US.
The Artificial Pancreas Clinical Trials

Clinical Trial History

2011
- JDRF-1 & JDRF-2: UVA, Padova, Montpellier, UCSB
- HCT-1: Stanford, UVA
- HCT-3: Stanford, UVA
  JDFF-Mount Sinai: Mayo Clinic
- NIH-2: UVA, Padova
  AP@Home-2: Padova, Montpellier, Amsterdam
- JDRF-3: UVA, UCSB, Stanford, Padova, Montpellier, Israel

2012
- DiAs introduced – 1st portable outpatient Closed-loop Control platform
- Pilot trials in Padova and Montpellier

2013
- HCT-2: Stanford, UVA
- NIH-1: UVA, Padova
  AP@Home-1: Padova, Montpellier, Amsterdam

2014
- NIH-3: UVA, Stanford

2015
- NIH-4: UVA Project Nightlight
- NIH-5: UCSB, UVA, Mayo, Padova

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# The Road To The “Closed Loop”

<table>
<thead>
<tr>
<th>First Generation</th>
<th>Second Generation</th>
<th>Third Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

## First Generation
- **Very-Low-Glucose Insulin Off Pump**
  - Pump shuts off when user not responding to low-glucose alarm

## Second Generation
- **Hypoglycemia Minimizer**
  - Predictive hypoglycemia causes alarms, followed by reduction or cessation of insulin delivery before blood glucose gets low
- **Hypoglycemia/ Hyperglycemia Minimizer**
  - Same product as #2 but with added feature allowing insulin dosing above high threshold (e.g. 200 mg/dL)
- **Automated Basal/Hybrid Closed Loop**
  - Closed loop at all times with meal-time manual-assist bolusing
- **Fully Automated Insulin Closed Loop**
  - Manual meal-time bolus eliminated

## Third Generation
- **Fully Automated Multihormone Closed Loop**

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**Northwestern University Feinberg School of Medicine**
Conclusions

- Technology has become standard of care for Diabetes management in T1DM and T2DM
- Improvement in HbA1c and Reduction of hypoglycemia
- The fully automated closed loop is very close (2017)
Thank You