Diabetes Technology
Objectives

To review emerging diabetes technology, including:

- Continuous Glucose Monitoring (CGM)**
- Basics of Insulin Pumps
- Insulin Pump and CGM Integration
- Artificial Pancreas/Hybrid Closed Loop Technology

** For in-depth details on CGM, see the slide library titled “Continuous Glucose Monitoring (CGM) in the Diabetes Resource Center
Diabetes Technology Timeline

- **Discovery of insulin (1921)**
- **First specialized insulin syringe (BD) (1924)**
- **Invention of first insulin pump (1963)**
- **Introduction of first insulin pen ‘Novopen’ (Novo Nordisk) (1985)**
- **Introduction of first-generation insulin pens (2000s)**
- **Introduction of artificial pancreas (2015)**
- **FDA approval for first ACE: t:Slim X2 insulin pump (2019)**
- **First Bionic Pancreas ‘iLet’ (2017)**
- **First hybrid closed-loop system, MiniMed 640G (2015)**
- **FDA approval for Tandem-Control-IQ AP (2020)**
- **First DIY-APS: Open APS system (2015)**
- **FDA approval for the first AP, MiniMed 670G insulin pump with Guardian 3 sensor (2017)**

- **Commercial production of artificial insulin ‘Iletin’ (1923)**
- **Launch of Novosyringe (Novo Nordisk) (1925)**
- **Introduction of the first commercial insulin pump (1979)**
- **Introduction of smart pumps (2010s)**
- **Introduction of second-generation insulin pens (2007)**
- **First Bionic Pancreas ‘iLet’ (2017)**
- **FDA approval for Tandem-Control-IQ AP (2020)**

Continuous Glucose Monitoring (CGM)
Monitoring Glycemic Control: Continuous Glucose Monitoring (CGM)

- With CGM, a small sensor is placed under the skin, to measure the interstitial glucose levels in intervals of 5 to 15 minutes\(^1\)
- CGM provides a more comprehensive assessment of glycemic control
- CGM can inform patients of impending glucose excursions using glucose trend arrows and influence treatment decisions\(^2\)
- CGM devices continue to become easier to use, more accurate, and more accessible to patients\(^2\)

Figure: Cengiz and Tamborlane. Diabetes Technol Ther. 2009. Jun;11 (Suppl 1)
Indications for CGM Therapy

**International Consensus:**
- All patients with T1D
- T2D treated with intensive insulin therapy, not meeting glycemic goals
- Those with problematic hypoglycemia

**AACE:**
- T1D with hypoglycemia/unawareness or not meeting glycemic goals
- T2D on intensive insulin therapy, high risk for hypoglycemia, or unappreciated hyperglycemia

**American Diabetes Association:**
- T1D not meeting glycemic goals (consider in T2D)
- Hypoglycemia/unawareness
- Sensor-augmented pump therapy
- Consider in pregnancy

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Current Commercially-Available CGM systems
No user calibration required

Only implantable CGM
Continuous Glucose Monitoring

• 3 types of CGM systems:
  • Real-time CGM
    • Provides continuous data on sensor glucose values, trends and alarms to the CGM receiver or smartphone
  • Intermittent scanned CGM
    • Glucose data and trend information are available after scanning the CGM sensor with the receiver or smartphone
    • Newer versions have real-time optional alarms
  • Professional CGM
    • A blinded CGM sensor is placed on the patient and worn for two weeks to obtain data on glucose values and trends
    • No real-time glucose data or alarms, only retrospective review of sensor glucose data
Key features of current personal CGM devices

<table>
<thead>
<tr>
<th>CGM Category</th>
<th>rt-CGM</th>
<th>is-CGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population Age (y)</td>
<td>≥2</td>
<td>≥2</td>
</tr>
<tr>
<td>Pregnancy Approval</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Warm-up time (h)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Sensor wear (d)</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Calibrations</td>
<td>None</td>
<td>2/d</td>
</tr>
<tr>
<td>Nonadjunctive Use</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Audible Alarms/Alerts</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Trend Arrows</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### Key features of current personal CGM devices

<table>
<thead>
<tr>
<th>CGM Category</th>
<th>Personal</th>
<th>rt-CGM</th>
<th>is-CGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexcom G6</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dexcom G5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Medtronic Guardian Connect Mobile</td>
<td>No</td>
<td>Yes</td>
<td>14-d system only (LibreLink)</td>
</tr>
<tr>
<td>Medtronic Enlite 2</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Senseonics Eversense</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Abbott Freestyle Flash Libre</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>share features</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pump integration</td>
<td>Tandem t:slim X2 with Basal IQ</td>
<td>Tandem t:slim X2</td>
<td>Medtronic Revel, 530G, 630G</td>
</tr>
<tr>
<td>Software Compatibility</td>
<td>Dexcom CLARITY Glooko Tidepool</td>
<td>Dexcom CLARITY Glooko Tidepool</td>
<td>Medtronic CareLink Tidepool</td>
</tr>
<tr>
<td>Acetaminophen Interference</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>MARD (%)</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Radiograph/MRI Compatible</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

- is-CGM = intermittent scanned CGM
- NA = not available
- rt-CGM = real time CGM

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Meta-analysis of CGM trials in T1D and T2D

Change in Hemoglobin A1C

Time in Target Glucose Range

Magnitude of reduction in time in hypoglycemia and CV according to baseline A1c with CGM

Published online 2019 Jun 27. doi: 10.1007/s11892-019-1177-7
Basics of Insulin Pump Therapy
What is Insulin Pump Therapy?

• Also called Continuous Subcutaneous Insulin Infusion (CSII)
• Allows for continuous administration of rapid-acting insulin analogs (i.e. aspart or lispro insulin) via a small subcutaneous plastic catheter that is changed every 2-3 days
• Insulin administration is based on insulin pump settings (basal rates, bolus dosing, corrective dosing) determined by the provider
Who is a candidate for insulin pump therapy?
Insulin Pump Guidelines: AACE

**Type 1 Diabetes**
- Not meeting glycemic control goals on MDI
- Especially those with:
  - High glycemic variability
  - Frequent severe hypoglycemia and/or unawareness
  - Significant “dawn phenomenon”
  - Extreme insulin sensitivity
- Consider for flexibility and QoL
- Special populations
  - Preconception, pregnancy
  - Children, adolescents
  - Competitive athletes

**Type 2 Diabetes**
- Select patients on insulin with any/all of the below:
  - C-peptide positive, but with suboptimal control on MDI
    - Note: CMS only covers insulin pump therapy for those who are c-peptide deficient
  - Substantial “dawn phenomenon”
  - Erratic lifestyle
  - Severe insulin resistance (candidate for U500 insulin by CSII)
  - Selected patients with other types of DM (e.g. post-pancreatectomy)

Insulin Pump Guidelines: Endocrine Society

**Type 1 Diabetes**
- With HbA1c above goal on MDI
- With continued hypoglycemia and glycemic variability, even if HbA1c is at goal
- Requiring lifestyle flexibility or improvement in QoL

**Type 2 Diabetes**
- With poor glycemic control despite intensive insulin therapy, oral agents, other injectable therapy, and lifestyle modifications

“as long as the patient and caregivers are willing and able to use the device”

Insulin Pump Guidelines: Other Considerations

Characteristics suggesting patient may not be a good candidate for insulin pump therapy:

- Unable/unwilling to perform MDI, recommended glucose testing or carbohydrate counting
- Lack of motivation to achieve tighter glucose control, history of non-adherence
- Concerns about pump therapy interfering with lifestyle
- History of serious psychological or psychiatric condition
- Unable to recognize the limitations of insulin pump therapy
  - Unrealistic expectations (e.g. the insulin pump will eliminate patient responsibility for diabetes management)
Anatomy of the Insulin Pump

**Reservoir**: insulin storage
- Between 200-300 units

**Tubing**: component of each insulin pump (except Omnipod)
- Connects insulin reservoir to infusion site

**Infusion site/cannula**: Small flexible plastic cannula inserted into SC tissue by a small retractable needle

**Reservoir**: insulin storage
- Between 200-300 units
Current Commercially-Available Insulin Pumps
Insulin Pump Settings

• **Basal Rate**
  - Continuous infusion of rapid-acting insulin to provide basal/long-acting coverage
  - Entered as units of insulin/hour and can be programmed to have different rates for different times of day
  - Temporary increases or decreases in basal rates can also be programmed

• **Insulin-to-Carb Ratio**
  - Used to calculate insulin bolus dose to cover carbohydrate/meal intake

• **Sensitivity Factor**
  - Used to calculate corrective insulin dosing for hyperglycemia

• **Target Glucose**
  - Entered as a single target glucose value or target glucose range (i.e. 90-150 mg/dL)
    - Corrects hyperglycemia using sensitivity factor at upper limit
    - Subtracts insulin from bolus dose if pre-meal blood sugar is under lower limit

• **Active Insulin Time**
  - Estimated duration of insulin action (usually 3-4 hours)
Advantages of Insulin Pump Therapy

- Ability to more closely approximate physiologic insulin secretion
- Ability to administer very small doses of insulin accurately
- Flexibility in insulin dosing to accommodate lifestyle needs (i.e. reduced basal rates for physical activity)
- Improved quality of life for many patients
- Improvement in glycemic control\(^1\)
- Reduction in rates of severe hypoglycemia and DKA\(^2\)

\(^1\) and \(^2\) – see references at end of slide deck.
Possible Disadvantages of Insulin Pump Therapy

• High cost, need for insurance coverage
• Labor-intensive
  • Site changes every 2-3 days
  • Close monitoring for any device/site malfunction
  • Maintaining adequate supplies
  • May not improve quality of life for some patients
• Appearance/Device wear
• Adhesive allergy
Integrating CGM and Insulin Pump Technology

- Insulin pump therapy can help improve glycemic control and reduce hypoglycemia, but it requires close monitoring and attention from the patient.

- The use of insulin pump and CGM technology together has progressed towards automated insulin delivery, where infusion of insulin is automated and driven by CGM glucose values.
Integrating CGM and Insulin Pump Technology

• Sensor-augmented pump (SAP) therapy
  • Use of insulin pump and CGM, but without cross-talk between them

• Threshold or low glucose suspend
  • Suspends insulin infusion at a predetermined glucose value

• Predictive low glucose suspend (PLGS)
  • Suspends insulin infusion prior to reaching threshold low glucose value

• Automated insulin delivery (AID) or Hybrid Closed-Loop (HCL)
  • Algorithm-based modulation of insulin infusion according to CGM glucose values and trends, including PLGS functions.
# Integrating CGM and Insulin Pump Technology

<table>
<thead>
<tr>
<th></th>
<th>Threshold suspend</th>
<th>Predictive-low glucose suspend</th>
<th>Automated Insulin Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medtronic</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>530G (SmartGuard)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>630G (SmartGuard)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>670G (SmartGuard)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Tandem</strong></td>
<td></td>
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<tr>
<td>t:slim X2 (Basal IQ)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>t:slim X2 (Control IQ)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Insulet</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Omnipod5/Horizon*</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*In phase 3 trial
Threshold Suspend

- **Multicenter RCT comparing SAP with or without TS therapy**
- T1D, age 16-70 years, A1C 5.8%-10%, used SAP for >6 months
- **Primary outcomes:**
  - Primary safety endpoint was change in A1C
  - Primary efficacy end point: AUC for nocturnal hypoglycemic events
  - Secondary end points: % sensor glucose values <70 mg/dL
- **Results:** Use of TS resulted in a significant decrease in nocturnal and overall hypoglycemia with no significant rise in A1C


A1C, hemoglobin A1C; AUC, area under the curve; RCT, randomized controlled trial; SAP, sensor-augmented pump; T1D, type 1 diabetes; TS, threshold suspend.
Threshold Suspend in the Real World

- **Retrospective analysis** of data from patients using MiniMed 530G to assess the effectiveness of TS feature in a real-world setting.

- Data from 20,973 patients analyzed for TS feature enabled (TS ON) vs not enabled (TS OFF) and daytime vs nighttime collection and %SG values indicating hypoglycemia and hyperglycemia were calculated.

- **Primary outcomes**: Hypoglycemia and hyperglycemia events as indicated by SG values during TS ON and TS OFF days.

- **Results**: TS use reduced hypoglycemia when used consistently.

Agrawal P et al. *Diabetes Technol Ther.* 2015 May;17(5)

SG, sensor glucose; TS, threshold suspend.

SG distributions in the hypoglycemic range for TS ON vs TS OFF days.
PROLOG Trial: Tandem t:slim with PLGS

- Multicenter, crossover RCT comparing SAP with and without PLGS system
- Enrollment criteria: age ≥6 years, T1D with insulin use ≥1 year, no medical contraindications to participation
- Primary outcome: % time SG<70 mg/dL in each 3-week period (SAP vs PLGS)
  - Secondary outcomes: % glucose <60 mg/dL, <50 mg/dL, AOC (70 mg/dL), low blood glucose index, and frequency of CGM hypoglycemic events
- Results: PLGS significantly reduced time with SG <70 mg/dL (overall 31% reduction) without increasing % time in hyperglycemia.

Forlenza et al. Diabetes Care 2018 Oct; 41(10): 2155-2161

AOC, area over the curve; CGM, continuous glucose monitoring; PLGS, predictive low-glucose suspend; PROLOG, PLGS for Reduction Of LOw Glucose; RCT, randomized controlled trial; T1D, type 1 diabetes; SAP, sensor-augmented pump; SG, sensor glucose.
Automated Insulin Delivery/Hybrid Closed-Loop (HCL) Technology

Hybrid Closed-Loop System: Medtronic 670G

- Approved US FDA September 2017 for patients with T1D ≥14 years old, then expanded to ages 7-13 years in June 2018\(^1\)
- Auto mode
  - Preset glucose target 120 mg/dL
  - Temp target of 150 mg/dL up to 12 hours
  - Adjustment of basal rate every 5 minutes
  - Requires announcement of meals/carbohydrates for bolus calculation
- Predictive low-glucose suspend
  - Stops insulin infusion up to 30 minutes before reaching your preset low limit
- Manual mode
  - Standard insulin pump settings

Medtronic 670G: Safety and Efficacy

- Single-arm, multicenter trial to evaluate safety and effectiveness of in-home HCL systems
- Patients enrolled were adolescents and adults with T1D with insulin pump therapy >6 months with or without CGM
- **Primary outcome:** A1C, improvement in time in target range, hypoglycemia
- **Results:** A1C, 7.7% (P<0.001) in adolescents and 7.3% (P<0.001) in adults; time in target range, 60.4 (P<0.001) in adolescents and 68.8 to 73.8 (P<0.001) in adults

### Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adolescents (N = 30)</th>
<th>Adults (N = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, N (%)</td>
<td>16 (53.3)</td>
<td>53 (56.4)</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>14 (46.7)</td>
<td>41 (43.6)</td>
</tr>
<tr>
<td>Age, mean ± SD, years</td>
<td>16.5 ± 2.29</td>
<td>44.6 ± 12.79</td>
</tr>
<tr>
<td>Weight, mean ± SD, kg</td>
<td>67.4 ± 12.98</td>
<td>79.9 ± 18.20</td>
</tr>
<tr>
<td>BMI, mean ± SD, kg/m²</td>
<td>23.7 ± 3.80</td>
<td>27.1 ± 5.42</td>
</tr>
<tr>
<td>Duration of diabetes, mean ± SD, years</td>
<td>7.7 ± 4.15</td>
<td>26.4 ± 12.43</td>
</tr>
<tr>
<td>TDD, mean ± SD, U/kg/day</td>
<td>0.8 ± 0.24</td>
<td>0.6 ± 0.20</td>
</tr>
<tr>
<td>HbA1C, mean ± SD, % (IQR)</td>
<td>7.7 ± 0.84 (7.1–8.4)</td>
<td>7.3 ± 0.91 (6.7–7.8)</td>
</tr>
</tbody>
</table>

A1C, hemoglobin A1C; BMI, body mass index; CGM, continuous glucose monitoring; hb, hemoglobin; HCL, hybrid closed-loop; IQR, interquartile range; SD, standard deviation; T1D, type 1 diabetes; TDD, total daily dose.
FIG. Sensor glucose profiles during the run-in and study phase. Median and interquartile range of sensor glucose values throughout the day and night, beginning at midnight (00, on x-axis), in (A) adolescents and (B) adults. The gray band and dotted line represent data from the run-in phase; the pink band and solid line represent data from the study phase.
Hybrid Closed-Loop System: Tandem t:slim X2 with Control-IQ

<table>
<thead>
<tr>
<th>Glucose Level</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 180 mg/dL</td>
<td><img src="https://www.tandemdiabetes.com/products/t-slim-x2-insulin-pump/control-iq" alt="Delivers" /></td>
</tr>
<tr>
<td>Above 160 mg/dL</td>
<td><img src="https://www.tandemdiabetes.com/products/t-slim-x2-insulin-pump/control-iq" alt="Increases" /></td>
</tr>
<tr>
<td>Below 112.5 mg/dL</td>
<td><img src="https://www.tandemdiabetes.com/products/t-slim-x2-insulin-pump/control-iq" alt="Decreases" /></td>
</tr>
<tr>
<td>Below 70 mg/dL</td>
<td><img src="https://www.tandemdiabetes.com/products/t-slim-x2-insulin-pump/control-iq" alt="Stops" /></td>
</tr>
</tbody>
</table>

Delivers an automatic correction bolus if sensor glucose is predicted to be above 180 mg/dL.

Increases basal insulin delivery if sensor glucose is predicted to be above 160 mg/dL.

Maintains active Personal Profile settings.

Decreases basal insulin delivery if sensor glucose is predicted to be below 112.5 mg/dL.

Stops basal insulin delivery if sensor glucose is predicted to be below 70 mg/dL.

Tandem HCL algorithm

• Multicenter RCT comparing SAP to closed-loop therapy with Control-IQ algorithm

• 168 patients with T1D > 1 year on insulin therapy, age 14-71 years, A1C 5.4%-10.6%

• Primary outcomes: Percentage of time in target glucose range (70-180 mg/dL)

• Results: Use of the Control-IQ closed-loop algorithm resulted in a greater percentage of time spent in target glucose range compared to SAP (71±12% vs. 59±14%, P<0.001).

Tandem Control-IQ HCL algorithm

- **Secondary Outcomes:**
  - Prespecified secondary outcomes included change in A1c and time with glucose <70 mg/dL, with results favoring the closed-loop group as below
  - The mean change in A1c was −0.33 percentage points (95% CI, −0.53 to −0.13; P = 0.001)
  - The mean difference in the percentage of time glucose level was less <70 mg/dL was −0.88 percentage points (95% CI, −1.19 to −0.57; P<0.001)

HCL Systems in Development: Omnipod5/Horizon

• Single-arm, multicenter observational trial evaluating safety and feasibility of OmniPod MPC algorithm in pediatric, adolescent, and adult patients with T1D

• Population: 6-65 years, T1D ≥1 year, A1C 6%-10% in past 6 months, insulin pump use ≥6 months, and total daily insulin dose >0.4U/kg

• Primary outcomes: % time sensor glucose was <70 mg/dL and % time in ≥250 mg/dL during HCL phase
  - Secondary endpoints: Sensor mean glucose, % time ≤50, ≤60, 70-140, 70-180, ≥180, ≥300 mg/dL, SD, CV of CGM values
  - Omnipod MPC algorithm was safe during day and night for all three populations; longer term studies will assess safety and performance under independent living situations in all ages

Do-It-Yourself Hybrid Closed-Loop Systems

- Medtronic 670G is the only first generation artificial pancreas system available
  - Several other systems are under evaluation in clinical trials¹
- Frustration with the slow pace of such trials has led to "looping" with DIY HCL systems, thus creating momentum for patient-led healthcare innovation¹
- An online community of “loopers” exists for support and can be found via the hashtag #WeAreNotWaiting¹
- DIY systems are not FDA approved, and in May 2019 the FDA issued its first-ever warning statement about their use²
  - This warning was based on a non-fatal accidental insulin overdose in a patient with T1D who used a DIY system
  - A joint statement from 3 online DIY system developers highlighted the fact that the warning was based on outcomes from a single patient who was outside of the US, and that the patient has since recovered

Do-It-Yourself Hybrid Closed-Loop Systems

- DIY systems are comprised of a compatible insulin pump, a CGM sensor and a third-party device, a microcomputer or a smartphone, that contains a system-specific algorithm¹
- The third-party device enables communication between the algorithm, insulin pump and the CGM sensor¹
- DIY systems are also referred to as “open-source,” as the algorithm and user instructions can be obtained without cost via the Internet¹
- Three main DIY systems are currently available¹:
  - OpenAPS
  - AndroidAPS
  - Loop
- A 2019 international survey of 209 caregivers of children and adolescents, representing the largest study of DIY APS users, reported improved glycemic control in all groups²


APS, artificial pancreas system;
Do-It-Yourself Hybrid Closed-Loop Systems

- Available DIY HCL Systems:
  - Open APS
  - Android APS
  - Loop

APS, artificial pancreas system; DIY, do-it-yourself; HCL, hybrid closed loop.

https://openaps.readthedocs.io/en/latest/docs/While%20You%20Wait%20For%20Gear/monitoring-OpenAPS.html
HCL Therapy in Sub-Optimally Controlled T1D

- **Open-label RCT to evaluate efficacy of HCL in improving glucose control and reducing hypoglycemia**
- **Patient enrollment criteria:** T1D, age ≥6 years, on insulin pump therapy, and A1C 7.5%-10%
- **Primary outcome:** Time in target glucose range (70-180 mg/dL) at 12 weeks
  - Secondary endpoints: A1C, SD and CV of glucose, % time in hypo- and hyperglycemia, AUC <3.5mmol/L, insulin requirements, bodyweight, and PedsQL score
- **Results:** TIR was significantly higher in the HCL group vs control group (65% [SD 8%] vs 54% [9%]; $P<0.0001$); A1C in HCL group was reduced from 8.3% (0.6%) to 7.4% (0.6%) after 12-weeks

HCL Therapy in Sub-optimally Controlled T1D

Advantages of closed loop therapy were more pronounced during the night.

<table>
<thead>
<tr>
<th>Day (0800 h to 2359 h)</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>Difference (95% CI)*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of time with sensor glucose level in range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.9–10.0 mmol/L</td>
<td>52% (10)</td>
<td>59% (9)</td>
<td>5.9 (3.1 to 8.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Less than 3.5 mmol/L</td>
<td>1.6% (0.9 to 2.7)</td>
<td>1.6% (0.9 to 2.1)</td>
<td>2.2% (0.9 to 2.8)</td>
<td>NA†</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>10.0 (1.2)</td>
<td>9.3 (0.8)</td>
<td>9.8 (1.0)</td>
<td>-0.51 (-0.77 to -0.24)</td>
</tr>
<tr>
<td>SD of sensor glucose, mmol/L</td>
<td>4.0 (0.6)</td>
<td>3.7 (0.5)</td>
<td>3.9 (0.5)</td>
<td>-0.26 (-0.40 to -0.12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Night (2400 h to 0759 h)</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>Difference (95% CI)*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of time with sensor glucose level in range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.9–10.0 mmol/L</td>
<td>54% (13)</td>
<td>77% (8)</td>
<td>21.5 (17.9 to 25.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Less than 3.5 mmol/L</td>
<td>1.8% (0.6 to 4.1)</td>
<td>1.0% (0.7 to 1.8)</td>
<td>2.2% (0.7 to 3.3)</td>
<td>NA†</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>9.5 (1.4)</td>
<td>8.0 (0.7)</td>
<td>9.4 (1.2)</td>
<td>-1.46 (-1.76 to -1.16)</td>
</tr>
<tr>
<td>SD of sensor glucose, mmol/L</td>
<td>3.6 (0.5)</td>
<td>2.9 (0.5)</td>
<td>3.6 (0.5)</td>
<td>-0.67 (-0.84 to -0.49)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or median (IQR). *Difference is closed-loop minus control. †p value not computed as 24-h result was not significantly different; thus, separate day and night comparisons were not done.

Table 3: Day-and-night glucose control during closed-loop and control periods

CI, confidence interval; IQR, interquartile range; NA, not applicable; SD, standard deviation; T1D, type 1 diabetes.
More time in range with HCL compared to other technologies

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Mean difference (95%CI) (95%Prl)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparisons</strong></td>
<td></td>
</tr>
<tr>
<td>CSII+CGM vs CSII+(CGM/FGM/SMBG)</td>
<td>1.83 (−4.33, 8.00) (−5.71, 9.38)</td>
</tr>
<tr>
<td>Closed loop vs CSII+CGM</td>
<td>10.60 (6.46, 14.74) (5.30, 15.90)</td>
</tr>
<tr>
<td>MDI+CGM vs MDI+CGM</td>
<td>−2.16 (−11.05, 6.73) (−12.82, 8.51)</td>
</tr>
<tr>
<td>MDI+FGM vs MDI+FGM</td>
<td>−2.69 (−12.97, 7.59) (−14.96, 9.58)</td>
</tr>
<tr>
<td>MDI+SMBG vs MDI+SMBG</td>
<td>−7.25 (−16.75, 2.25) (−18.62, 4.12)</td>
</tr>
<tr>
<td>Nocturnal closed loop vs CSII+CGM</td>
<td>6.73 (−0.22, 13.67) (−1.70, 15.16)</td>
</tr>
<tr>
<td>Closed loop vs MDI+CGM</td>
<td>8.77 (4.18, 13.35) (2.99, 14.54)</td>
</tr>
<tr>
<td>MDI+CGM vs MDI+CGM</td>
<td>−3.99 (−10.42, 2.44) (−11.84, 3.86)</td>
</tr>
<tr>
<td>MDI+FGM vs MDI+FGM</td>
<td>−4.52 (−12.81, 3.76) (−14.49, 5.45)</td>
</tr>
<tr>
<td>MDI+SMBG vs MDI+SMBG</td>
<td>−9.09 (−16.35, −1.82) (−17.88, 0.29)</td>
</tr>
<tr>
<td>Nocturnal closed loop vs MDI+CGM</td>
<td>4.89 (1.73, 8.05) (0.63, 9.15)</td>
</tr>
<tr>
<td>MDI+CGM vs Closed loop</td>
<td>−12.76 (−20.64, −4.87) (−22.26, −3.25)</td>
</tr>
<tr>
<td>MDI+FGM vs Closed loop</td>
<td>−13.29 (−22.71, −3.86) (−24.57, −2.01)</td>
</tr>
<tr>
<td>MDI+SMBG vs Closed loop</td>
<td>−17.85 (−26.42, −9.28) (−28.14, −7.56)</td>
</tr>
<tr>
<td>Nocturnal closed loop vs MDI+CGM</td>
<td>−3.87 (−9.46, 1.71) (−10.77, 3.02)</td>
</tr>
<tr>
<td>MDI+FGM vs MDI+CGM</td>
<td>−0.53 (−5.77, 4.70) (−7.03, 5.97)</td>
</tr>
<tr>
<td>MDI+SMBG vs MDI+FGM</td>
<td>−5.09 (−8.47, −1.72) (−9.57, −0.62)</td>
</tr>
<tr>
<td>Nocturnal closed loop vs MDI+CGM</td>
<td>8.88 (1.71, 16.05) (0.20, 17.57)</td>
</tr>
<tr>
<td>MDI+SMBG vs MDI+FGM</td>
<td>−4.56 (−8.88, −0.25) (−10.05, 0.92)</td>
</tr>
<tr>
<td>Nocturnal closed loop vs MDI+SMBG</td>
<td>9.41 (0.30, 18.52) (−1.50, 20.33)</td>
</tr>
</tbody>
</table>

Heterogeneity variance = 0.81
Specific Metrics to Consider in Hybrid Closed-Loop Therapy

- Duration of report: 14-day windows are standard
- % sensor usage
- % time in range, 70-180 mg/dL (goal ≥70%)
- % <70 mg/dL (goal ≤4%)
- % <54 mg/dL (goal ≤1%)
- Assess mean glucose (mg/dL)
- Assess glucose variability with CV (goal <36%)
- Assess time in HCL (goal >80%)

- Reasons listed for HCL exits
- Average basal delivery in HCL vs preset basal rates (units)
- Frequency and patterns of basal suspensions
- Frequency of correction boluses
- Use of setpoint changes for activity or sleep
  - Medtronic 670G: Temp target of 150 mg/dL
  - Tandem X2 with Control:IQ: Exercise or Sleep mode with modified target range

Summary

• Advances in CGM technology and closed loop systems coupled with open source algorithms have transformed diabetes management
• New metrics for assessing glycemic control are emerging to accommodate advances in technology and will help guide glycemic control targets
• DIY hybrid closed loop systems have enabled a more patient-driven approach to disease management, but are not FDA approved
• While insurance coverage for diabetes technology is expanding, the high cost of this technology may still not be feasible for many patients

CGM, continuous glucose monitoring; DIY, do-it-yourself; FDA, Food and Drug Administration.
Contributors

- AACE would like to thank the following clinicians for their contributions.
  - Dr. Georgia Davis, MD
  - Dr. Francisco Pasquel, MD, MPH
  - Dr. Archana Sadhu, MD, FACE
References


References

# Common Acronyms (Diabetes)

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Meaning</th>
<th>Acronym</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>HEMOGLOBIN A1C</td>
<td>CGM</td>
<td>Continuous Glucose Monitoring</td>
</tr>
<tr>
<td>AGP</td>
<td>Ambulatory glucose profile</td>
<td>CV</td>
<td>COEFFICIENT OF VARIATION</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under curve (in reference to a graphic)</td>
<td>DIY</td>
<td>Do-it-yourself</td>
</tr>
<tr>
<td>Avg</td>
<td>Average</td>
<td>eA1C</td>
<td>Estimated hemoglobin A1C</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
<td>FDA</td>
<td>Food and Drug Administration (United States)</td>
</tr>
</tbody>
</table>
## Common Acronyms (Diabetes)

<table>
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<tr>
<th>Acronym</th>
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<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMI</td>
<td>Glucose management indicator</td>
<td>OAD</td>
<td>Oral antidiabetic drugs</td>
</tr>
<tr>
<td>HCL</td>
<td>Hybrid Closed-loop</td>
<td>PLGS</td>
<td>Predictive low-glucose suspend</td>
</tr>
<tr>
<td>Hb</td>
<td>Hemoglobin</td>
<td>Rt</td>
<td>Real time</td>
</tr>
<tr>
<td>I</td>
<td>Integrated</td>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
<td>T1D</td>
<td>Type 1 Diabetes</td>
</tr>
<tr>
<td>MAGE</td>
<td>Mean amplitude of glucose excursions</td>
<td>T2D</td>
<td>Type 2 Diabetes</td>
</tr>
<tr>
<td>MODD</td>
<td>Mean of daily differences</td>
<td>TDD</td>
<td>Total daily dose</td>
</tr>
</tbody>
</table>