RESEARCH UPDATE: CLOSED LOOP/ARTIFICIAL PANCREAS

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May 6, 2015

Conflicts of Interest Disclosure

- Certified pump trainer for Animas, Medtronic MiniMed, Omnipod, Roche, & Tandem Diabetes
- CGM trainer for Dexcom & Medtronic MiniMed
- Advisory Board Member, Unomedical
- Advisory Board Member, Halozyme
- Member of the Lilly Educator Network

Objectives

1. Be able to describe how the closed loop/artificial pancreas system works.
2. Be able to describe the limitations of the closed loop/artificial pancreas system.
3. Be able to describe at least 2 research studies using closed loop/artificial pancreas technology and discuss the results.
Components of the Closed Loop/Artificial Pancreas (CL/AP) System

- Insulin Pump
- Glucose Sensor
- Control Algorithm

- Proportional-Integral-Derivative (PID, ePID)
- Model Predictive Control (MPC) / Multiple Model Predictive Control (MMPC) / Multiple Model Probabilistic Predictive Control (MMPPC)
- Fuzzy Logic (FL)
- Others

Doyle et al., Diabetes Care, 2014
ePID Algorithm

- Components:
  - Proportional
  - Integral
  - Derivative
  - Insulin on board (IFB)
- One size fits all model

Model Predictive Control (MPC) Algorithm

- Has both Predictive and Adaptive modes and decides when is best to use each
- Learns the needs of each individual pump user
- Flexible, can include things that are a function of time of day (meals, exercise, etc.)
- Easier to adapt to the user than the PID algorithm
- Sometimes semi-closed loop
  - Pre-bolusing seen as more beneficial

Fuzzy Logic (FL) Algorithm

- Does not use differential equations to determine insulin dose
- Takes other physiological parameters into account, such as illness and stress
- Allows for personalized dosing for each individual patient
Comparison of the Algorithms

Figure 2. Performance of algorithms averaged over the nine study enrolled subjects. Red shaded MPC is the M3NPC strategy. The B7 control value represented above indicates the mean glucose for that algorithm (dotted line). The 30 mg/kg glucose dose represents a simulated postprandial glucose challenge. The glucose levels were estimated using the fbGlucose model. Each algorithm was evaluated for 84 h in a random order. The algorithms were validated in silico using the ACCINI and control. IMPC, artificial pancreas control; MPC, model predictive control; BB, basal-bolus.

Early CL/AP Studies

Findings of Early Studies
- Insulin only CL/AP systems
- Able to maintain tighter glycemic control
- Still had some hyperglycemia and post-prandial hypoglycemia
Limitations of the Insulin-Only CL/AP System

- Insulin
  - Quick-acting insulins still slower than what is needed to maintain blood glucose in the 70-180 mg/dl range

- Sensor accuracy
  - Up to 20 min lag time between blood glucose and sensor glucose readings (now better, 1-10 min lag time)
  - Sensor generally less accurate on day 1, improves with time

- Software
  - Reactive systems – glucose rises first, and then more insulin is given
  - Newer algorithms working on overcoming this limitation

Other Limitations of the CL/AP System

- Real estate
- Number of devices to carry
- Start-up/calibration time

Research Findings To Date
**Multihormonal Studies**

- Attenuating hypoglycemia – Glucagon
- Minimizing postprandial hyperglycemia
  - Pramlintide (Symlin)
  - Exenatide (Byetta)
  - Liraglutide (Victoza)
  - Others

**CL/AP with Glucagon**

- **Goal:** Attenuate hypoglycemia

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**CL/AP with Glucagon: Challenges**

- Glucagon stability
- Multiple infusion devices required
CL/AP with Pramlintide

- **Goal:** minimize post-prandial hyperglycemia
- Renukuntla et al.
- 10 subjects (50%M)
- Average age $23.2\pm1.0$ years old
- Average baseline HbA1c = $7.3\pm0.3\%$
- **Results:**
  - Pramlintide (30 µg) delayed but did not significantly decrease peak postprandial glucose.
  - Less prandial insulin administered ($p=NS$)
  - No glucagon suppression
- **Conclusion:** Pramlintide not the best option for a bihormonal CL/AP system

CL/AP with Pramlintide

- **Goal:** minimize post-prandial hyperglycemia
- Weinzimer et al.
- 8 subjects (50%M)
- Age 15-28 years old
- Average baseline HbA1c = $7.5\pm0.7\%$
- **Results:**
  - Pramlintide (30 µg) delayed ($p<0.0001$) and also decreased peak postprandial glucose by an average of $25\, mg/dl$ ($p=0.006$)
  - Significant differences in premeal insulin levels ($p<0.05$)
- **Conclusion:** Beneficial results seen with Pramlintide in the CL/AP system

CL/AP with Pramlintide: Challenges

- Variable results
  - +/- significant differences in peak postprandial glucose
  - +/- significant differences in amount of insulin administered
  - No glucagon suppression
  - Must be injected SQ with every meal
  - Tolerance to pramlintide believed to develop over time
**CL/AP with Exenatide**

- **Goal:** minimize post-prandial hyperglycemia
- **10 subjects (50%M)**
- **Average age 23.2 ± 1.0 years old**
- **Average baseline HbA1c = 7.3 ± 0.3%**

**Results:**
- Exenatide (2.5 µg) significantly decreased peak postprandial glucose (p<0.03)
- Less prandial insulin administered (p=NS)
- Exenatide suppressed endogenous glucagon response (p<0.03)

**Conclusion:** Adjuvant therapy with exenatide in the CL/AP setting effectively decreases postprandial hyperglycemia, blunts glucagon response, and may decrease prandial insulin requirements without causing undue hypoglycemia.

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**CL/AP with Exenatide: Challenges**

- Separate SQ injection, multiple times per day
- Dose used for the study is not available by pen

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**CL/AP and Exercise**

- Early exercise studies (insulin only) still resulted in hypoglycemia
- Insulin + glucagon minimizes exercise-induced hypoglycemia
  - Bionic Pancreas study
  - Newer studies propose adding heart rate monitoring to further minimize exercise-induced hypoglycemia
    - 12 subjects
    - 9/10 exercise intensity
    - Pilot study, p=NS for all measures, but looks promising
CL/AP and Dining Out, with/without wine

- 24 adults with T1DM
- Overnight closed loop control using MPC algorithm
- Medium meal and large meal with alcohol (wine) both tested
- Overnight CL/AP control resulted in tighter glycemic control and less hypoglycemia

CL/AP and Dining Out, with/without wine (contd.)

EATING OUT: Profiles (medians and interquartile ranges) of plasma glucose and insulin concentrations and insulin infusion in eating out scenario (12 participants).

EATING IN: Profiles (medians and interquartile ranges) of plasma glucose and insulin concentrations and insulin infusion in eating in scenario (12 participants). Outlying squares represent hypoglycemic events (glucose level <54 mg/dl).

CL/AP and Dining Out, with/without wine (contd.)

96 of plasma glucose values in range and out of range in both eating in and eating out scenarios, combined. Percentages represent total time plasma glucose level was below, at, and above target from midnight until the end of the closed loop delivery.

Figure 3. From Hovorka et al., BMJ, 2011.
Overnight Control with CL/AP

- Overnight at diabetes camp – 56 subjects 10-18 yrs old – BG’s much better with less hypoglycemia on CL/AP (Phillip & Battelino, NEJM, 2013)
- Multiple overnights on CL/AP – 10 subjects age 46.4 ± 8.5 yrs old – spent more time in target range of 80-140 mg/dl overnight, awoke with a lower fasting glucose, and had better control then next day (Brown et al., Diabetes Technology & Therapeutics, 2015)

CL/AP @ Home Simulation Study

- Multicenter European study
- 13 adults, average age 45 ± 14 yrs old, HbA1c = 7.4 ± 0.9%
- Open loop x1 day then closed loop x1+ days (42 hrs); only overnight analyzed
- Study done in hotel to simulate “at home” experience
- Results: when on CL/AP system spent more time in target glucose range (70-180 mg/dl); 84% vs 62% (p=0.04) and less time in hypoglycemia (2% vs 10%, p=0.01)
- Conclusions: CL/AP system is safe and efficacious in an at home setting, and results in more time in range and less time with hypoglycemia
**CL/AP @ Home: First Outpatient Studies**

- Multicenter, multi-national randomized insulin only CL/AP crossover study
- 18 subjects completed study, age 46 ± 10 years, baseline HbA1c = 7.4 ± 0.7%, 76% M (13/20)
- Results: less time spent in hypoglycemia and less risk of hypoglycemia on CL/AP, slightly higher overall glucose average (161 vs. 152 mg/dl)
  - Higher overall glucose average attributed to emphasis placed on avoiding hypoglycemia.
- Conclusion: Closed loop control via smartphone in the outpatient setting is safe and effective. Further optimization of the control algorithm is necessary to both minimize hypoglycemia and not compromise overall glycemic control.

**CL/AP @ Home: Glucagon**

- Beacon Hill Study:
  - 20 adults & 32 adolescents
  - Wore CL/AP system for 5 days in the outpatient setting
  - Lived in a restricted area during intervention part of study
  - Always accompanied by study personnel
  - No restrictions on food or exercise, alcohol limited to low/moderate intake
- Results:
  - Average BG = 138 mg/dl
  - Only 4.8% (adults) & 6.1% (adolescents) of time spent with BG < 70 mg/dl
- Conclusion: Better glycemic control with less hypoglycemia with a bihormonal artificial pancreas in both adolescents and adults.

**CL/AP @ Home: Glucagon**

- Beacon Hill study done on children/adolescents in a summer camp setting, Summers 2013 & 2014
  - Controlled real-life clinical laboratory
  - 2013: 32 adolescents & young adults, 12-20 years old
  - Wore CL/AP with glucagon 15 days
  - 160 full days of real-life CLAP data collected
  - 2014: 19 children 6-11 years old, 4,560 hrs of data collected
- Anecdotal results:
  - “Yes. I trusted it. It works. If you check it, it’s perfect. My blood sugars are perfect.”
  - “It’s like a vacation from diabetes.”

Future Directions

- Smarter insulin pumps
  - Ex. – GlucoSitter software in Medtronic pump – fully closed loop (at least 3 generations away)
- Warming insulin infusion site
- Faster insulins
- Addition of other hormones to the system
- Creation of a more stable glucagon
- Implanted/internal CL/AP systems
- Better Algorithms

Product photos courtesy of Insuline Medical (1&2) and Renfrew Group InSmart (3), via Google Images
What Users Want

- System improvements
  - Smaller devices
  - Greater sensor accuracy
  - Faster insulin

- #wearenotwaiting
  - Open source software and devices that communicate with multiple platforms – basically mix & match your own system

- Bigfoot Medical [link](http://www.healthline.com/diabetesmine/bigfoot‐family‐their‐diabetes‐and‐homemade‐closed‐loop‐system#1)
- DIYPS (Do‐It‐Yourself‐Pancreas‐System) [link](http://diyps.org/)

Conclusion

Conclusions

- The CLAP system improves glycemic control and time that glucose is in range while minimizing hypoglycemia compared to open-loop systems
  - True for any time of day
  - True for all age groups (tested in as young as 3 years old)
  - Newer systems/algorithms are more efficacious than earlier systems
  - At‐home systems now available for testing
  - All algorithms have their benefits
  - Multi-hormonal system is likely the best model
  - Faster insulins, more improved sensors, and stable, easy to administer adjuvant hormones (e.g., glucagon) are needed
  - Timeline is always longer than anticipated
  - People with diabetes want the solution now, and are working to create their own platforms
  - First at-home systems may be available to the general public as early as 2018**
References