Full Carbohydrate Consumption with Hybrid Closed-Loop Control of Insulin Delivery for Type 1 Diabetes - A Case Report

Robert S. Silvers, S.M. and Christine Tsien Silvers, M.D., Ph.D.
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Abstract

Using five variations of hybrid closed-loop insulin pump controllers plus a conventional pump during a four-month period, a 48-year old male with Type 1 diabetes was able to lower his hemoglobin A1c (A1C) from 8.7% to 6.0%, both without increasing his rate of hypoglycemia, and while consuming an average for each system configuration of up to 259 grams of carbohydrate per day. The percentage of time that the patient's blood glucose level was in the 60-180 mg/dL range and the average estimated A1C from Dexcom continuous glucose monitor data[1] were 75%/6.3% with normal Medtronic 530G insulin pump use, 88%/6.1% with a Beta Bionics iLet using both insulin and glucagon, 86%/6.5% with a Beta Bionics iLet configured to use insulin only, 89%/5.6% for a system called OpenAPS version oref0, 92%/5.5% using OpenAPS version oref1, and 91%/5.6% using a system called Loop version 1.4. This seemingly similar performance greatly diverges when adjusted for carbohydrate consumption by dividing average daily carbohydrate by the estimated A1C. Using this metric of average carbohydrates per A1C, the highest-performing closed-loop system of the five systems described was Loop version 1.4, which outperformed by 89% the lowest-performing system, Beta Bionics iLet using insulin only. Overall, the case report demonstrates that a patient with Type 1 diabetes using a closed-loop insulin pump system not only can safely lower his A1C, but furthermore can also consume moderate to high amounts of carbohydrate while maintaining tight blood glucose control.

Background

A 48-year-old male was diagnosed with Type 1 diabetes mellitus in 1988 at the age of 19. For the first 14 years, his diabetes was controlled using multiple daily injections of regular insulin and NPH. Approximately 15 years ago, he began using a Medtronic insulin pump with Novolog and Humalog. Over the years, he has used various continuous glucose monitoring systems, including the Gluco Watch, Freestyle Navigator, Dexcom G4, Medtronic Enlite, Dexcom G5, and Senseonics Eversense. His body mass index (BMI) lifetime high was 24.6. He became much more physically active in 2011, participating in regular fitness activities including running and cycling. His BMI during the most recent five years has been approximately 21.5.

Closed-Loop "Artificial Pancreas" Systems

The closed-loop "artificial pancreas" has been a milestone in the treatment of type 1 diabetes, with many types of systems being developed and being worked on toward commercial availabilty.[2] The Medtronic 670G is the only currently commercially-available, FDA-approved, closed-loop insulin pump. A 2016 pivotal trial[3] established that among 124 patients, A1C went from an average of 7.4% to 6.9% while using this system. Time within the range of 70-180 mg/dL blood glucose levels increased from 66.7% to 72.2%. Carbohydrate consumption was not established for that trial.

The patient has used three types of hybrid closed-loop insulin delivery systems in which the user enters carbohydrate intake information. One system was a pre-production unit planned for future commercial release called the Beta Bionics iLet, which was used while the patient participated in an FDA-sponsored trial. The second was a homemade system based on the OpenAPS open-source project that is not currently planned to become an FDA-approved medical device. The third was an open-source iPhone app called Loop. The iLet and OpenAPS systems were each tried in two different configurations. This case report presents results from use of those five different hybrid closed-loop insulin delivery systems as well as from use of an open-loop system consisting of a commercially-available insulin pump and a separate commercially-available continuous glucose monitor.

Description of the Beta Bionics iLet

The Beta Bionics iLet is a hybrid closed-loop system under development for potential commercial distribution with the goal of being simple to use while being able to work with either single or dual hormones.[4] The iLet user interface (Figure 1) provides a history of blood glucose levels. Menu options allow the user to enter meal size in descriptive terms, such as "typical," or "less than typical." Over time, the iLet system learns what those terms mean for a particular user. There are additional controls for specifying an elevated blood glucose target to help prevent hypoglycemia during moments of activity. Setting up the iLet system requires only that the care provider enter the user's weight in kilograms. Everything else is learned by the system as the system is used. The system learns in an ongoing manner, with significant learning over the first 18 hours; after several more days, the system stabilizes. The patient found that one advantage of a self-learning system is that the chances for a setup error are minimized.

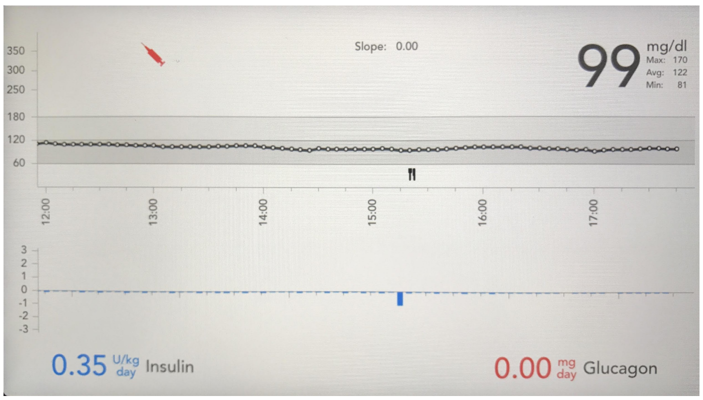

Figure 1: iLet closed-loop system interface

Description of OpenAPS

OpenAPS is one of several "do-it-yourself" closed-loop solutions for insulin delivery. Using open-source tools, the patient self-assembled a non-FDA-approved wireless insulin-pump controller as pictured in Figure 2. The user interface is primarily provided by an iPhone running software called Nightscout, which is an open-source project for the purpose of remote monitoring of blood glucose levels and treatment information. Nightscout runs on a cloud-computing platform, such as Heroku or Azure, and can be used to monitor dependents, such as children, when they are away from their parents' immediate care.

OpenAPS can be built using several different types of hardware.[5] The patient used an Intel Edison wearable Linux computer, a Hamshield brand Explorer board (that powers the Edison and provides a 915 MHz radio link to the Medtronic pump), and a self-designed and 3D-printed enclosure. Because Medtronic disabled certain wireless features in its newer insulin pumps, an older pump that has firmware version 2.4a or lower had to be used. The hardware is powered by a 2500-mAh lithium battery, which provides approximately 16 hours of battery life. The wireless range is typically less than 30 feet.

Figure 2: OpenAPS hardware in enclosure designed by the patient

One typically uses OpenAPS by manually entering carbohydrate content using the standard Medtronic pump "Bolus Wizard," which then triggers an insulin bolus. The system uses the radio link to query the pump's history, to recognize that a bolus was given, and to know the pre-programmed basal rates within the pump. Software running on the Edison Linux computer uses these pump settings as a starting point, but can alter them up or down by a user-configurable maximum change. The algorithms employed by OpenAPS have evolved over time. An earlier version is called oref0, and a later version is called oref1; the primary difference is that oref0 only alters basal rates temporarily, whereas oref1 can more quickly provide insulin through micro-boluses.[6] Over time, the OpenAPS system adapts and will suggest new default pump settings for basal rates, carbohydrate ratios, and sensitivity factors. For this to work well and to work in a safe manner, the user has a responsibility to enter correct carbohydrate information. This feature is of great benefit to the skilled user, but most people cannot count carbohydrates accurately,[7] which can lead to potential problems. For example, Dr. Howard Wolpert, M.D., a former senior physician at the Joslin Diabetes Center in Boston and author of Smart Pumping (American Diabetes Association, 2002), has found that for an apple with 30 grams of carbohydrate, carbohydrate-counting patients have guessed the apple to have anywhere from 10 to 60 grams of carbohydrate. For this reason, it is best for the user to weigh his/her food, or enter information directly from the nutritional label on pre-packaged food.

Description of Loop

The final system tested is called Loop, an iPhone app that can control some older Medtronic insulin pumps through a small Bluetooth-based hardware interface.[8] Because the app is not approved by Apple or the FDA, it is only distributed in source-code form; in order to use Loop, then, one must build the app using a Macintosh computer, as well as purchase an Apple iOS developer license to install the app on an iPhone. Loop version 1.4 was used for this testing.

The controller that Loop uses for pump communication is called RileyLink, and, as seen in Figure 3, is small and unobtrusive. It uses an 850-mAh lithium-ion battery to provide for about 30 hours of battery life. The range between the RileyLink and the pump varies, but generally the system works well if the two are within about ten feet. For software, the Loop main user interface, as seen in Figure 4, is complete and does not rely on additional software such as NightScout for input or visualization. Loop will upload treatment data to NightScout if desired, which can be used for remote monitoring of a patient, or for statistics and analysis of past results.

Loop can receive blood glucose data from several sources – Medtronic Enlite, G4 Share, G5, or Apple Health. Loop accepts carbohydrate input either from a meal-entry button press (not pictured), or it will automatically "see" food input from Apple Health as provided by a separate diet app. When food information is entered, Loop will suggest an insulin bolus; if the bolus is accepted, Loop will instruct the pump to dose it. It is not necessary to bolus from the pump itself, which is helpful for people who do not want their pump seen by others.

Figure 3: Patient-created custom enclosure

When carbohydrate information is entered, one can also select the estimated number of hours required for carbohydrate absorption. This is simplified with pictograms representing types of food, such as fruit or pizza. If one were to select a fast-acting source of carbohydrate, Loop would be more likely to recommend the entire bolus up front. In contrast, if one were to select pizza, for example, Loop would be more likely to recommend an initial partial bolus, using a dual-wave method to spread out the remainder of the dose.

In either case, specifics are dependent on how much insulin and carbohydrate Loop thinks that the patient has ingested, and what it predicts for the patient's resulting blood glucose level. Furthermore, via clicking on the carbohydrate portion of the interface, Loop will display the previously entered food entries and their actual estimated absorption times.

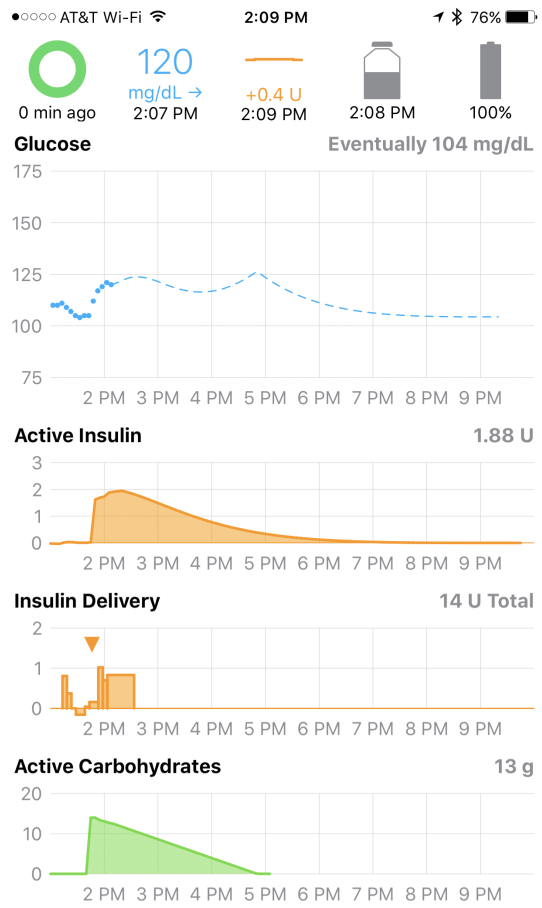

Figure 4: Loop user interface

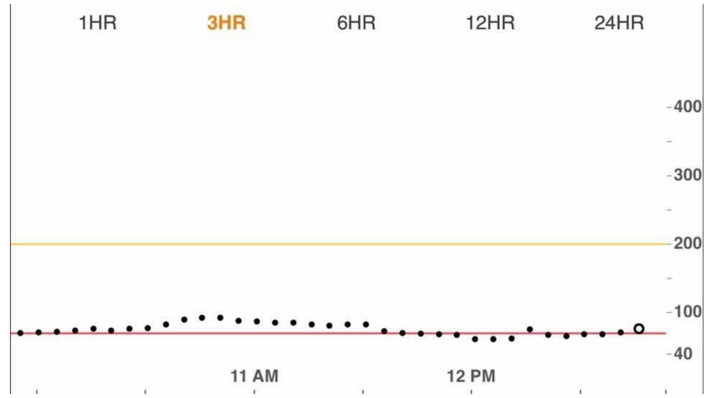

Figure 5: Glucose levels before, during, and after two ice cream bars

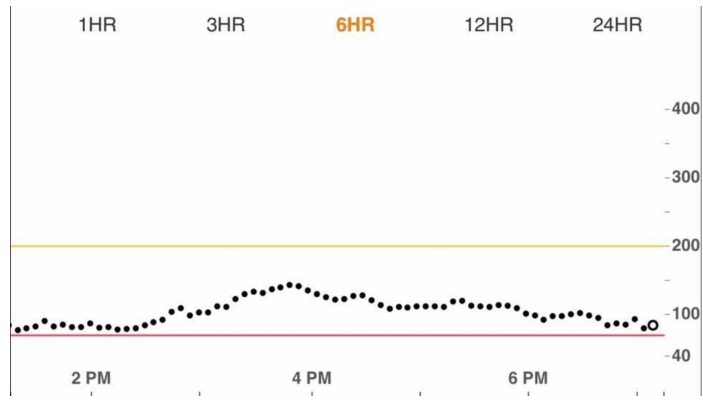

Figure 6: Glucose levels before, during, and after a very large meal

Extreme Carbohydrate Testing

Due to the need for safety for a wide range of users of all different experience levels, the iLet is optimized to avoid hypoglycemia at all costs. That means that it provides a smaller bolus than what is typically needed, and then cautiously adds more insulin as time goes on. Because of this difference between the partial bolus that the iLet gives, and the optimal amount required based on the carbohydrate consumed, there is an ever-increasing disparity as the size of a meal increases. The patient experimented with very high carbohydrate meals with the iLet, but these meals consistently resulted in a high blood glucose level, even after a week of system training. Because OpenAPS and Loop allow the user to manually bolus using the pump controls, and because these systems take over insulin dosing to help correct for any error, there is no practical limit to what the user can have for meal size or type while still maintaining a normal range of blood glucose levels.

Furthermore, when a closed-loop system maintains optimal basal rates, control is better and bolusing becomes easier. For one, the overnight fasting glucose levels tend to become perfected. Waking up at 90-100 mg/dL became routine and expected during this testing. Suddenly one-third of the day is at a blood glucose level that brings down the average A1C value. Also, well-tuned basal insulin control makes eating a high-carbohydrate meal much more feasible. Figure 5 shows that it is possible with OpenAPS to eat two ice cream bars with 52 grams of carbohydrate and 39 grams of fat total during the day, with results the same or better as a person without diabetes. Figure 6 shows Loop processing 185 grams of carbohydrate from two McDonald's Big Macs, two McDonald's Blueberry & Crème pies, and a 6-ounce strawberry yogurt smoothie.

System	Date Start	Date End	Carb (g)	Calories	Carb % of Diet	Est. A1C	Std Dev	% < 60 mg/dL	% > 180 mg/dL	% in Range	Carb / Std Dev	Carb / A1C
90 days before	1/1/17	3/31/17	N/A	N/A	N/A	7.4	66.1	3	39	58	N/A	N/A
Open-loop normal pump	4/13/17	4/26/17	221	1993	44.4	6.3	53.8	5	20	75	4.1	35.1
iLet-insulin/ glucagon	4/27/17	5/10/17	159	1974	32.2	6.1	45.9	1	11	88	3.5	26.1
iLet-insulin only	5/11/17	5/24/17	115	1856	24.8	6.5	41.5	0	14	86	2.8	17.7
OpenAPS-oref0	5/25/17	6/7/17	218	2401	36.3	5.6	39.9	5	6	89	5.5	38.9
OpenAPS-oref1	6/8/17	6/21/17	238	2450	38.9	5.5	36.8	3	5	92	6.5	43.3
Loop 1.4	8/15/17	8/29/17	259	2403	43.1	5.6	37.1	3	6	91	7.0	46.3

Figure 7: Table of results

As meals get larger, the impact of fat on insulin requirements becomes more significant, especially when a meal contains over approximately 40 grams of fat. One research study found that for high-fat meals, an additional 42% of insulin was needed for the same amount of carbohydrate.[9] This additional insulin cannot be given with the initial main bolus, as it would very likely cause hypoglycemia. The patient found that very high-fat meals would result in elevated glucose levels beginning 1.5 to 2.5 hours after the start of the meal. With OpenAPS, the method used to combat that rise was to watch the glucose levels from the Dexcom, and then provide a post-meal bolus of about 40% of the carbohydrate value, or to treat 80-90% of the fat grams as carbohydrate, using a simplified version of the Pańkowska et al. method of factoring fat and protein into the dosing requirements.[10,11] With Loop, this additional fat-as-carbohydrate quantity was entered at the time of the meal, but could be manually specified to be delivered two hours later. Loop would then add additional insulin as required. The next section demonstrates some high-carbohydrate examples of what the patient found to be possible with a system that has this type of flexibility.

Excerpts from High-Carbohydrate Testing Log

Here are some examples of well-controlled high-carbohydrate eating from the testing that was done during this patient-initiated self-study.

June 7th, 2017 (OpenAPS). Three slices of Papa Gino's large sausage pizza (99 grams of carb, and 54 grams of fat). The highest BG was 136 from the pizza. Two cookies, Focaccia bread, Not Your Average Joe's Backyard Burger, Ice Cream. 279 grams of carb. 2738 calories. Mean glucose 113. Standard deviation 26.9. Estimated equivalent A1C for day: 5.6%.

June 18th, 2017 (OpenAPS). Orange juice, instant oatmeal, eight Oreo cookies, Pancakes, maple syrup, banana, blueberries, two Filet-o-Fish, 10 pieces sushi/rice, cheesecake, green beans, eggplant. 406 grams carb. 2879 calories. Stayed below 183 glucose. Mean blood glucose 121. Standard deviation 31.3. Estimated equivalent A1C for day: 5.8%.

June 19th. 2017 (OpenAPS). 303 grams of carb and 140 grams of fat - which included Life cereal, blueberries, two Filet-o-Fish, two McDonald's Blueberry & Crème pies, two 12" flour tortillas, six slices of cheddar cheese. 2872 calories. Mean glucose 108, standard deviation 34.1, estimated equivalent A1C: 5.4%

Aug 20th, 2017 (Loop). Two containers of Greek yogurt, two Filet-o-Fish, one applesauce, pasta and meatballs, two McDonald's Blueberry & Crème pies, Häagen Dazs ice cream bar. 254 grams of carb, 104 grams of fat, 2354 calories. Mean glucose 96, standard deviation 25.6, estimated A1C: 5.0%.

Results

The chart in Figure 7 shows data and results from 90 days prior to the patient's period of self-study, the two-week period of using an open-loop system (via a Medtronic pump and a Dexcom continuous glucose monitor), two weeks of using the iLet with insulin and glucagon (target blood glucose level 100 mg/dL), two weeks of using the iLet with insulin only (target blood glucose level 110 mg/dL), two periods of two weeks each of using OpenAPS (target blood glucose level 90 mg/dL), and a two-week period of using Loop (target blood glucose level 90-100 mg/dL). The last column of the chart shows the relationship between average carbohydrates consumed per day and estimated equivalent A1C from using each system. A larger number is indicative of being able to eat a larger amount of carbohydrate while maintaining a lower A1C.

Key Clinical Information

	Most Recent Value	Your Target/Goal	Previous Value
Hemoglobin A1c (%)	**6.00** on 08/31/2017		8.70 on 03/31/2017
Weight (lbs.)	**146.60** on 08/31/2017	0.00	150.00 on 03/31/2017

Figure 8: Image from the patient's self-disclosed medical report

The patient found that it was best to eat carbohydrate in moderation with the iLet; in doing so, the result was an estimated equivalent A1C within the "6.5% or below" most strict guidelines commonly recommended for people with Type 1 diabetes[12] while having a very low rate of hypoglycemia. With OpenAPS, the patient was able to eat a larger amount of carbohydrate while attaining an even lower estimated A1C, but at a higher risk and rate of hypoglycemia. With Loop, the patient's average carbohydrate-to-estimated-A1C ratio was even higher, representing the best overall results of the six methods described when adjusting for carbohydrate intake.

Conclusion

The iLet has the ability to be life-changing once available due to ease of use and the ability to allow a patient to think much less about how to manage his/her diabetes. Automating the correction of blood glucose levels will also mean more sleep, which is important for quality of life. The iLet system, if used as directed, seems likely to have the potential of enabling anyone to attain a 6.5% or lower A1C, with a low risk of hypoglycemic episodes, provided that he/she moderates his/her carbohydrate intake.

For those who are highly motivated, who would like to use a closed-loop system prior to the iLet's becoming available, and who prefer much more control—although with higher responsibility and higher risk of hypoglycemia—one can construct one's own hybrid closed-loop insulin delivery system. While these homemade systems have not been proven to be safe by the FDA, the presented patient's results demonstrate that each system, once properly tuned, is able to facilitate the ability to eat as much carbohydrate as a person without diabetes might consume, while still having a reasonable chance of achieving an A1C below 6%.

In the described patient case, various hybrid closed-loop insulin delivery systems used over a 90-day period lowered the patient's A1C by approximately 37%, from 8.7% to 6.0% (Figure 8). Moreover, the patient did not experience a greater percentage of low glucose readings—hence, experienced no greater risk of hypoglycemia—while averaging up to 259 grams of carbohydrate per day. This represents a normal amount of carbohydrate for someone without Type 1 diabetes consuming 2000 calories per day.[13] This lowering of A1C levels was possible because the standard deviation, or swings in blood glucose throughout each day, were reduced by almost 60%.

In conclusion, it is possible for individuals with longstanding Type 1 diabetes to eat foods in an unrestricted manner (i.e., including high-carbohydrate foods) while having tight blood-glucose control, provided they use the latest tools, not all of which are currently commercially available. While not a cure, these devices provide highly flexible treatment options that make good control of blood glucose and the resulting lower A1C values not only possible, but also possible without having to eat a carbohydrate-restricted diet.

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