The Artificial Pancreas in 2016: A Digital Treatment Ecosystem for Diabetes

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With the increasing availability of continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII), the artificial pancreas (AP) (the commonly accepted term for closed-loop control [CLC] of blood glucose [BG] levels in diabetes) has become a hot area in translational research and industrial development. After a prolonged period of inpatient, clinical research center trials using cumbersome systems, the field has progressed rapidly over the past 2 years to long-term, free-living studies running AP algorithms on smartphones. Although it is still not a cure, the AP is the most promising advance in the treatment of diabetes at this time.

This issue of *Diabetes Care* presents today's AP state of the art, including reports on multinational home-use AP trials, studies in young children, the use of multihormonal approaches to mitigate meal-related hyperglycemia, and discussions of AP study designs and outcome measures. This collection of articles establishes the AP as a new diabetes treatment paradigm—not a single-function CGM or CSII device but an adaptable wearable network encompassing the patient in a digital treatment ecosystem.

In its May 2014 issue, *Diabetes Care* featured the progress in the AP field in a series of articles labeled "Advances in Artificial Pancreas Development." In addition to an editorial discussing the state of the art of AP development in 2014 (1), the issue included original articles that covered a broad range of topics including analyses of the possible physiological inputs to CLC (2), real-time estimation of insulin sensitivity from CGM and insulin pump data (3), engineering of the AP algorithms (4), reports of predictive low-glucose suspend (LGS) systems (5), studies of overnight CLC at home (6), feasibility of the AP in type 2 diabetes (7), and the first around-the-clock outpatient CLC running a model predictive control (MPC) algorithm on a portable AP system (8).

Since then, *Nature*, *Science*, *JAMA*, the *New England Journal of Medicine*, and *Lancet* have published overviews or research articles on the AP as well (9–15). These articles supported the conviction that a mechanical solution to the problem of maintaining strict control of diabetes without increasing the risk of hypoglycemia was rapidly progressing to a reality.

HISTORICAL PERSPECTIVE

Although the AP concept can be traced back to studies in the 1970s that showed the possibility for external BG regulation using intravenous infusions of insulin and glucose and frequent BG measurements (16,17), today's AP was made possible by advances in insulin pump technology and the introduction of real-time, minimally invasive CGM sensors (18–21). The pioneering AP study by Steil et al. (22) in 2006 was followed by a series of promising, short-term, closely supervised, inpatient investigations that demonstrated the effectiveness of hybrid CLC using manual premeal bolus dosing (23), tested different control algorithms (24,25) and the feasibility of a bihormonal "bionic" pancreas that used glucagon to prevent postmeal hypoglycemia resulting from aggressive premeal insulin (26), and demonstrated other benefits of CLC (27–30). Most of these reports showed the superiority of CLC over CSII therapy in terms of *1*) increased time within target BG range (typically 70–180 mg/dL), *2*) reduced incidence of hypoglycemia, and *3*) better overnight control (31). These studies were supported by the JDRF Artificial Pancreas Project Consortium and the National Institutes of Health AP initiatives, which set the stage for the European AP@home Consortium launched in 2010.

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See accompanying articles, pp. 1127, 1135, 1143, 1151, 1161, 1168, 1175, and 1180.

SYSTEM INTEGRATION

LGS, which is now commercially available and is already a part of clinical practice, was the first half-step to CLC because it is an integrated pump and CGM system that can automatically shut off insulin delivery when sensor glucose levels fall below a preset low threshold level. The Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial showed a 38% reduction in nocturnal hypoglycemia compared with CGM alone, without increasing HbA_{1c} (32). Predictive LGS algorithms, which have the ability to shut off insulin delivery based on the projected fall of sensor glucose levels during a predefined time interval, brought this type of system to a higher level of computational sophistication when introduced in 2014. However, both of these LGS approaches are based on a simple switch to turn off insulin in response to falling glucose values and lack the defining characteristics of CLC—feedback/feedforward modulation of insulin delivery based on the analysis of glucose fluctuations and insulin on board.

OUTPATIENT CLC

The first step toward CLC in the outpatient setting was using a laptop-based system installed at the bedside of children at a diabetes camp (12). Other AP trials, which confirmed the feasibility of CLC outside of the hospital in adults and adolescents, used small personal computers installed in the patients' homes (6,14,33). The University of Virginia group introduced the first wearable AP platform—the Diabetes Assistant (DiAs)—in 2011. DiAs used an Android smartphone as a computational hub, and its defining characteristic was the ability to switch smoothly between different modes of operation depending on patient preference and signal availability (34,35). Several international multisite trials confirmed the feasibility and the safety of this system in the outpatient setting (36–40).

AP TODAY

This issue of *Diabetes Care* presents the AP state of the art today and includes four reports on outpatient clinical trials in free-living patients: two testing the AP in adults (41,42), one in adolescents (43), and one in young children (44). One study examined whether adjunctive treatment with pramlintide and liraglutide improves CLC by mitigating postmeal glucose excursions (45) and one focused on the head-to-head comparison of two strategies: MPC and proportional integral derivative (PID) under comparable clinical conditions (46). The issue concludes with two articles related to study design issues: a consensus document aimed at identifying a minimal set of outcome measures that should be included in future studies (47) and an article that discusses design considerations for AP pivotal trials (48). Here we provide a brief guided tour on these contributions by pointing out some relevant information for each article, which should help the reader put them into context.

Anderson et al. (41) report the results of a multicenter multinational trial testing the free-living use of a wearable AP system in 30 adults, aged 18–66 years, recruited in six centers in the U.S., Italy, France, and Israel. This nonrandomized study included three 2-week periods. In the first period, the patients used a sensor-augmented pump (SAP). In the second period, they used the AP system only overnight (from 2300 to 0700 h). In the third period, they used the AP 24/7. This study used the University of Virginia's DiAs AP platform.

Renard et al. (42) report a nonrandomized extension phase, continuing a previous AP trial (15) that tested, in free-living conditions, SAP against AP used from dinner to wake-up (evening-and-night AP). In the current study, the same AP system is used 24/7 for 1 month (day-and-night AP) in adults from the previous study (15). Day-and-night AP was compared against evening-and-night AP and SAP. The algorithm was an MPC algorithm developed at the University of Pavia, University of Padova, and University of Virginia. The algorithm was running on DiAs.

Tauschmann et al. (43) report the first outpatient trial testing in free-living, at-home day-and-night closed-loop insulin delivery in 12 adolescents, aged 15.4 ± 2.6 years, recruited in Cambridge, U.K. This randomized crossover study included two 1-week periods during which patients used either SAP or the AP. The control algorithm used was the MPC algorithm developed at the University of Cambridge. The algorithm was running on the Florence D2A wearable platform that was developed at the same university.

Del Favero et al. (44) report the results of the first study focused on outpatient day-and-night use of a single-hormone AP in 30 children, aged 5–9 years, recruited in five Italian centers and studied in a pediatric camp. This randomized crossover study included two 3-day periods during which the patient used either SAP, managed by their parent/caretakers, or SAP. The algorithm was an MPC algorithm developed at the University of Pavia, University of Padova, and University of Virginia. The algorithm was running on DiAs.

Sherr et al. (45) investigated clinical strategies that used adjunctive treatment with pramlintide and liraglutide, titrated to full therapeutic doses over 3–4 weeks, to blunt exaggerated postprandial glucose excursions. In the pramlintide study, two 24-h closed-loop inpatient studies were conducted in 10 subjects, aged 16–23 years. It compared AP alone with AP plus 60-μg doses of pramlintide given with each meal. A similar study was carried out with liraglutide in 11 subjects, aged 18–27 years, who were studied before and after treatment with daily injections of 1.8 mg of liraglutide. Meals were not announced in either study.

Pinsker et al. (46) compare two widely used AP control algorithms, personalized MPC and PID, under nonideal but comparable clinical conditions. The comparison was performed in 20 adults studied in a randomized crossover trial held in supervised inpatient 27.5-h AP sessions. Challenges included both announced (dinner and breakfast) and unannounced meals (lunch).

The current issue of *Diabetes Care* is enriched by a consensus document by Maahs et al. (47) in which a broad panel of scientists working in the field of the AP identified a minimal set of outcome measures that should be included among those presented when reporting on AP studies. This consensus on outcome measures will facilitate the interpretation of study results by investigators, regulatory bodies, health care providers, payers, and patients themselves, thereby accelerating the widespread adoption of AP technology.

Finally, Russell and Beck (48) discuss design considerations for AP pivotal studies intended to provide the necessary data to gain clearance from the U.S. Food and Drug Administration, coverage by payers, and adoption by patients and clinicians. In particular, a key aspect of study design is emphasized: the intervention to be used by the control group.

Suggested options are the currently available best technology, SAP, or the usual care.

Patients often ask how many years will it be before AP systems become commercially available for the treatment of their diabetes. Although there is still much work to be done in improving these systems, our readers should be reassured by the remarkable progress that has been made during the two years since *Diabetes Care*'s last AP issue. However, the evidence provided in the articles published in this special issue of *Diabetes Care* should not be interpreted as an indication that we are nearing the end of AP development. Rather, this body of work indicates that the translation of advances in AP technology into better care for patients with diabetes is just around the corner.

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