The Artificial Pancreas: Are We There Yet?

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"Are we there yet?" How many parents have heard this phrase time and time again when traveling with young children eager to arrive at a much-anticipated vacation spot, but who are clearly tiring of the travel. The response from the parents is always a reassuring "no, but we are getting very close." As parents, we then think about how we can use this as a teaching moment to have our children understand that they should enjoy the moment at hand. So, we then reflect on quotes we have heard in the past such as life being a journey, not a destination, and then tell our children they should focus on the travel itself and that getting there is half the fun. We think this is a perfect analogy of the status for closed-loop technology and the artificial pancreas. But, now, it is not the children asking "are we there yet?" but the parents who can only dream that such a technology will be available for their children with diabetes who have to face the ever-present threat of severe hypoglycemia and diabetic ketoacidosis, while struggling to incorporate advances in technology, such as continuous glucose monitoring, into the management of their children's diabetes. This is where many want the "journey" to end and hope we, as a medical community, finally arrive at the "destination," which is indeed the commercial availability of a truly effective artificial pancreas.

There has been remarkable progress made to date in regard to closed-loop technology as the safety and efficacy have been reported in both outpatient and inpatient clinical trials. Given the incredible interest in this topic and its importance to clinical care, this issue of *Diabetes Care* features a comprehensive selection of articles devoted to the development of the artificial pancreas, including a two-part Bench to Clinic series, two randomized trials, and three additional studies that provide new information on the technology (1–7).

We recognize that many readers are somewhat familiar with the concept of an artificial pancreas, but would not be so familiar with all the technologic, algorithmic, and physiologic parameters required for such a device or with all the current limitations. In brief, the closed-loop system refers to a feedback-controlled device with an algorithm that automatically adjusts the rate of insulin delivery by an insulin pump based on real-time continuous glucose monitoring data (3). In this issue, we feature a two-part Bench to Clinic narrative to provide the relevant background for understanding such a system (1,2). In the Bench narrative, Kudva et al. (1) provide "an in-depth understanding of insulin-glucose-glucagon physiology in conditions that mimic the free-living situation to the extent possible in type 1 diabetes that will help refine and improve future closed-loop system algorithms." They discuss the metabolic perturbations that need to be addressed and better defined in order to design improved systems, including postprandial glucose excursions, exercise, stress, intercurrent illness, dawn phenomenon, sex steroids, and hypoglycemia, among others. In the Clinic narrative that follows, Doyle et al. (2) compare and evaluate technology used in current closed-loop systems "to gain further momentum toward outpatient trials and eventual approval for widespread use." They address the challenges involved in development of the artificial pancreas and provide the proposed minimal common requirements for future clinical trials. The summary of clinical trial protocols from 2010 to 2013 and the discussion of recent clinical advancements are incredibly educational as they demonstrate the evolution of this field. The authors conclude that with the "effective integration of engineering and medicine, the dream of automated glucose regulation is nearing reality" (2). Like the parents of children with type 1 diabetes, we sincerely hope that this statement is true.

The University of Cambridge group, led by Dr. Roman Hovorka, has been particularly productive. Kumareswaran et al. (3) provide the results of the first

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clinical trial of a closed-loop system in patients with type 2 diabetes. Using a crossover design in 12 subjects with non-insulin-treated type 2 diabetes, 24-h glucose profiles during closed-loop control were compared with corresponding levels during the control admissions, when the usual diabetes regimen was continued. The authors observed that 24 h of closed-loop control increased overall median time in the target plasma glucose range for the individuals with type 2 diabetes and suggested there was a greater benefit overnight.

The overarching objective of this program of technology development is to have systems that can be easily and safely employed by large numbers of patients at home. In this issue, Hovorka et al. (4) also provide a report on unsupervised use of a closed-loop system in adolescents with type 1 diabetes. This study also used an open-label, randomized, crossover design that compared sensor-augmented pump therapy with and without overnight closed-loop insulin delivery. As outlined, "the study was performed in real-life conditions," and as designed, the subjects were evaluated "with unrestricted diet and normal school and sporting activities and without telemonitoring or continuous supervision" (4). The authors report that the overnight closed-loop control increased the overall time in target range by ~15%, reduced mean overnight glucose levels by 14 mg/dL, and reduced the frequency of episodes of hypoglycemia, defined as sensor glucose levels below 63 mg/dL for at least 20 min. It was concluded that "unsupervised home use of overnight closed loop in adolescents with type 1 diabetes is safe and feasible" (4) and is associated with improved glucose control during the day and night and with fewer episodes of nocturnal hypoglycemia.

The remarkable progress in closed-loop technology has been the result of step-by-step improvements in pump and senor hardware, as well as advances in controller algorithms. This issue includes three additional reports regarding novel information and advances in the field. In the novel communication by Del Favero et al. (5), the authors used a meal-informed model predictive control strategy in outpatients to reduce postprandial glycemic excursions. In addition, Schiavon et al. (6) describe a means to estimate insulin sensitivity with use of the subcutaneous continuous glucose monitoring sensor and insulin pump. Finally, Beck et al. (7) assessed the effect of overnight insulin pump suspension in an automated predictive low glucose suspend system on morning blood glucose and ketone levels. Their findings demonstrated that "routine measurement of blood or urine ketones during use of an automated pump suspension system using continuous glucose monitoring, whether threshold based or predictive, is not necessary" (7). These findings confirm and extend those of Sherr et al. (8) that were also reported in a recent issue of *Diabetes Care*.

As clinicians who treat people with diabetes, the prevention and cure of this condition remain our ultimate goal. In the meantime, the great promise of an automated artificial pancreas system for insulin-treated type 1 and type 2 diabetic patients is that close to optimal control could be achieved with a marked reduction rather than an increase in the burdens of diabetes care. As illustrated by the articles in this issue of *Diabetes Care*, the "journey" toward the launching of a commercially available artificial pancreas is exciting. But, honestly, no one will be celebrating until we make it to the "destination" (i.e., the commercial availability of a truly effective artificial pancreas). So, are we there yet? Not quite, but in this regard, we should consider that it is *not* the journey, but the destination that matters.

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