EDITORIAL (SEE CHOUDHARY ET AL., P. 2023)

Closing the Loop: Another Step Forward

To achieve normoglycemia in people with diabetes, the complex hormonal and neuronal influences that regulate glucose homeostasis must be understood and addressed. In addition to insulin deficiency, abnormalities include dysregulation in the secretion and/or action of glucagon, incretins, and other counterregulatory hormones. Efforts to restore normal metabolism in diabetes with insulin therapy alone have been suboptimal, with hypoglycemia being a major problem. Pancreatic transplantation is restricted by the availability of the human pancreas and the risks of immunosuppressive therapy. The implantation of normal islets has met with limited success. The alternative approach, the creation of an artificial pancreas, is now a major area of active investigation.

An automated mechanical glucose-responsive sensor-guided insulin infusion system has been a long-term goal. Although significant challenges remain, with improvements in pump therapy and sensor technologies, considerable progress has been made over the past 5 decades. Feasibility studies using delivery of intraperitoneal insulin with implanted pumps and guided by subcutaneous glucose sensors have been successfully conducted in a small number of patients (1). Since insulin is secreted into the portal circulation, this approach has the advantage of more physiological insulin delivery and reduced peripheral hyperinsulinemia. Few studies have administered insulin via intraportal or intraperitoneal routes because they require invasive procedures, and there are concerns about complications such as infections.

Subcutaneous insulin pump therapy with real-time continuous glucose monitoring (CGM), an "open-loop" system, is now used in selected individuals for the management of type 1 diabetes. In appropriate people, improved glycemic control and reduction (but not elimination) of hypoglycemia can be realized with the use of these devices (2). Commercially available CGM devices measure glucose levels in interstitial fluid rather than blood glucose levels. Significant and variable lag times can occur, particularly when blood glucose levels are rapidly changing, contributing to problems with accuracy. Current systems also rely on the user to frequently review sensor values and respond appropriately (2,3). This limits the effectiveness of these systems, particularly in pediatric populations and in individuals with less motivation or with cognitive impairment (as occurs during hypoglycemia). User errors, poor detection of alarms during sleep, and complacency with frequent alarming for hypoglycemia are problems with the current systems. These issues support the need for the development of control algorithms that automatically and accurately alter insulin infusion rates to achieve normal glucose levels during fasting, eating, activity, and daily stress. Accommodations for individual differences in insulin sensitivity and pharmacokinetics are necessary, and it is imperative to incorporate safety features to avoid serious hypoglycemia. The acceptance by the U.S. Food and Drug Administration (FDA) of computer-based simulation studies (in silico testing) (instead of animal trials) has helped to more rapidly advance control algorithm development over the past several years (4,5). Sophisticated mathematical models and associated complex control algorithms, communication systems, and safety features are being developed to "close the loop" between the sensor and insulin infusion device (5–10) (http://consortium.jaeb-diabetes.net). Model systems are currently being tested in pediatric and adult individuals with type 1 diabetes—including during pregnancy—with encouraging results (11–13).

The first commercially available closed-loop system, the Biostator, was developed over 40 years ago (14). This large bedside device was primarily used for research purposes and required continuous venous glucose sampling with intravenous delivery of insulin and glucose. Since then, large bedside systems using intravenous blood sampling and automatic insulin and/or glucose infusions have been used infrequently in inpatient settings (15).

To help most individuals with diabetes, efforts have concentrated on the development of smaller, inexpensive, reliable, easy to use, comfortable, discreet, wearable systems that use minimally invasive (or ideally noninvasive) CGM that communicate accurately and wirelessly to subcutaneous insulin infusion systems. Control of postprandial hyperglycemia remains a challenge due to the pharmacokinetics of subcutaneous insulin absorption when compared with glucose absorption with a meal. In a study by Weinzimer et al. (16), a semiautomated hybrid system using a small priming premeal bolus assisted in better providing mealtime glycemic insulin coverage.

Whereas the achievement of normoglycemia is the goal, the avoidance of hypoglycemia is essential. Sophisticated control algorithms are trying to address this problem. Another approach to avoiding hypoglycemia is to use pumps that deliver both insulin and glucagon (17,18). In pilot studies, the addition of glucagon reduced hypoglycemia. Future work in this area will require the development of a stable form of glucagon suitable for outpatient use and better understanding of optimal dosing and frequency of delivery of glucagon.

Suspension of insulin infusion for actual or predicted hypoglycemia takes us another step forward in closing the loop. Pilot closed-loop feasibility studies lasting up to 24 h have reported promising results in lessening hypoglycemia (6,10,12,19). Hovorka et al. (11) studied a manual closed-loop insulin infusion system (nurse adjusted insulin pump settings, suspending infusion per algorithm) in children and adults to reduce nocturnal hypoglycemia.

In this issue of *Diabetes Care*, Choudhary et al. (20) report the results of a pilot study using an automated insulin pump system with a low glucose suspend (LGS) feature in an outpatient setting. Subcutaneous insulin infusion is suspended automatically for up to 2 h when hypoglycemia is detected by CGM if the user does not respond to the alarm. Adults with type 1 diabetes ($n = 31$) were evaluated for 2 weeks with the LGS feature turned off and for 3 weeks with the LGS feature turned on. Success in reducing nocturnal hypoglycemia was demonstrated in those individuals with the most hypoglycemia at baseline, and participant acceptance was high. Several limitations are acknowledged. Sensor inaccuracy remains an issue, as insulin delivery was suspended in some subjects in the absence of hypoglycemia (4/43 episodes; 2 with sensor error

alerts). Current sensors have reduced accuracy at low glucose levels, and improvements are still needed in predicting hypoglycemia. Two participants withdrew during run-in "due to difficulty using sensors," and one did not activate the LGS feature. This reminds us that minimization of user error is essential in the design of these systems.

The automated insulin shut-off feature to reduce severe nocturnal hypoglycemia represents an important step forward, but barriers for widespread use remain. Suspension of insulin must be closely regulated to avoid both hypoglycemia and ketonemia. Continued improvement in CGM is required, including greater sensor accuracy, reliability, and longevity. Systems need to be designed with better algorithms to take into account lag times in glucose sensing from interstitial fluids and the pharmacokinetics of subcutaneous insulin absorption. Responding to changes in glucose levels due to food ingestion, exercise, and stress remain challenges. Meter accuracy is still problematic since meter glucose values are used to calibrate current CGM systems. The use of glucagon in future insulin pump systems ("dual pumps") may also help reach the goal of achieving normoglycemia without severe hypoglycemia.

The article in this issue is an encouraging step forward in the development of an artificial pancreas. There is hope that a closed-loop system is within our reach, but more work needs to be done. An intravascular device for both glucose sensing and insulin delivery is needed that is easy and safe to both implant and use, and can be made available at a reasonable cost. Finally, cost-effectiveness studies and better reimbursement programs are also necessary. With many groups working collaboratively to advance these technologies, our patients should gain access to better tools in the foreseeable future.

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