EDITORIALS

Toward Automated Insulin Delivery

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For patients with type 1 diabetes, achieving the glycemic target recommended by the American Diabetes Association remains challenging, despite the use of insulin pumps, sensors for continuous glucose monitoring, the combination of these technologies (sensor-augmented pump), and systems that automatically suspend insulin delivery when glucose values fall below or are about to reach a prespecified threshold (low-glucose and predicted-low-glucose suspend features, respectively).[1]

The artificial pancreas, also called the closed-loop system, is a further step toward automated insulin delivery, addressing both hypoglycemia and hyperglycemia. It consists of an insulin pump, a glucose sensor, and an algorithm that continuously modifies the rate of insulin infusion on the basis of input from the sensor. Sensors may need fingerstick calibration or may be factory-calibrated. Closed-loop systems can deliver just insulin (single hormone) or insulin plus glucagon or another hormone (dual hormone). Closed-loop systems are called "hybrid" if they automatically adjust basal insulin but require patients to manually input carbohydrate consumption and bolus delivery.

Two recent meta-analyses of randomized, controlled trials comparing closed-loop and conventional pump therapy or sensor-augmented pumps in children, adolescents, and adults with type 1 diabetes showed that the closed-loop approach appears to be relatively safe and increases the percentage of time with glucose in the target range without increasing the risk of hypoglycemia.[2,3] To date, a single hybrid closed-loop system has been approved in the United States and the European Union, the Medtronic Minimed 670G, a single-hormone closed-loop system that modulates basal insulin delivery but does not administer automated boluses.

In an article now published in the *Journal*, Brown and colleagues present the results of a 6-month multicenter, 2:1 randomized trial assessing the efficacy and safety of a new hybrid closed-loop system, the Tandem Control-IQ,[4] as compared with a sensor-augmented pump (without a predicted-low-glucose suspend feature). The new system relies on a calibration-free sensor (Dexcom G6) and uses an algorithm with a dedicated hypoglycemia safety module, automated correction boluses, and an intensified program of nocturnal insulin delivery to achieve near-normal glycemia in the morning. The authors compared the performance of the closed-loop system with that of the sensor-augmented pump in 168 outpatients ranging in age from 14 to 71 years with basal glycated hemoglobin levels of 5.4 to 10.6%. They found that the use of the closed-loop approach increased the percentage of time with glucose levels in the target range (70 to 180 mg per deciliter [3.9 to 10 mmol per liter]) from 61% at baseline to 71% at the end of the trial, a change that was evident from the end of the first month. Improved glucose control was achieved throughout the day and — especially important — during the second half of the night. Conversely, in patients wearing a sensor-augmented pump, the time spent in range remained at 59% throughout the trial. Other outcomes, such as percentage of time that the glucose level was greater than 180 mg per deciliter or less than 70 mg per deciliter, the mean glucose level, variability in glucose level, and glycated hemoglobin level all favored the closed-

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loop system. There was one episode of ketoacidosis in the closed-loop group, due to pump infusion set failure, and no serious hypoglycemic events occurred in either group.

These results are impressive and clinically relevant, since it has been shown that for each 10% reduction in the time spent in the glucose target range, the risk of development or progression of retinopathy increases by 64% and the risk of development of microalbuminuria by 40%.[5] Furthermore, the fact that these results were obtained in patients of different ages and degrees of diabetes control adds robustness to the data. However, the trial was performed in university-based diabetes centers, and the baseline use of sensors and insulin pumps was higher than in the general population of patients with diabetes. Furthermore, the insulin pumps used in the group with the sensor-augmented pump lacked the ability to suspend insulin for predicted hypoglycemia.

The closed-loop system is becoming a mature technology ready for practical use, but there are a variety of barriers to a fully automated closed-loop system, including slow subcutaneous absorption of insulin, low stability of present glucagon formulations, insufficient sensor accuracy, and algorithms that are not yet flexible enough for everyday needs.[6] Whether closed-loop systems can be used in higher-risk patients, such as those with impaired awareness of hypoglycemia, also remains a pressing issue. Cost-effectiveness, user acceptance, and training of both patients and health care professionals also need to be addressed. It is clear that patients would appreciate wearing devices that require minimal interaction, leading to a more carefree lifestyle. We are not there yet, but the trial by Brown et al. offers an almost fingerstick-free option, providing a big step toward a brighter future for patients.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Understanding Progressive Fibrosing Interstitial Lung Disease through Therapeutic Trials

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In the era before antifibrotic therapy, idiopathic pulmonary fibrosis (IPF), the most common of the idiopathic interstitial pneumonias, had a survival rate of 20 to 30% at 5 years,[1] a poorer outcome than that of many common forms of cancer. Patients with IPF still have a progressive course that is either gradual and predictable or defined by sudden episodes of acute worsening. The lethality of this disease has stimulated substantial interest in identifying new therapeutic options for its management, with two new therapies showing clinical benefit in the past 5 years.[2,3]

Similar patterns of decline have also been observed in other forms of diffuse parenchymal lung disease. This finding has led to the description of chronic fibrosing interstitial lung disease as a distinct category of advanced lung disease.[4,5] In survey data, this phenotype is thought to have a poor prognosis, similar to that of IPF,[6] although epidemiologic studies of this cohort are limited. Treatment efficacy in this group is un-

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