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COMMENTARY

Clinical Hurdles and Possible Solutions in the Implementation of Closed-Loop Control in Type 1 Diabetes Mellitus

Howard Zisser, M.D.

Abstract

From an engineering perspective, controlling blood glucose appears to be a fairly straightforward single input (glucose), single output (insulin) control problem. Unfortunately, mimicking Mother Nature turns out to be a complex endeavor. The primary hurdle in developing a useful, safe closed-loop control algorithm for an artificial pancreas is the time delays associated with current continuous glucose monitors and subcutaneously delivered insulins. This article will provide a brief history of the artificial pancreas, outline the main clinical hurdles restricting its current implementation, and list possible solutions for success.

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Introduction

A system that has a single input and a single output, minimal external disturbances, and minimal delays is easy to model and control. Unfortunately, type 1 diabetes mellitus (T1DM) is not that type of a system. Patients with T1DM have an insufficient supply of insulin. Insulin, a hormone produced by beta cells of the pancreas, allows glucose to be used as a fuel by the cells of the body. This challenging control problem of automating insulin delivery in order to control blood glucose would have been solved a long time ago if there were no time delays associated with glucose sensing and insulin action and patients with T1DM did not eat, exercise, or experience illness and stress. Type 1 diabetes mellitus, with current glucose sensing and subcutaneous insulin replacement, represents a sluggish system with multiple disturbances that tend to pull blood glucose concentration away from the optimal normoglycemia target.

History of the Artificial Pancreas

As early as 1959, Professor E. Perry McCullagh, an endocrinologist at the Cleveland Clinic, demonstrated the concept of an implantable artificial endocrine pancreas. The closed-loop regulatory system, which consisted of a glucose monitoring device, transmitter, and insulin syringe, was looked upon as the future treatment device for diabetes. In the mid 1970s, closed-loop control was accomplished with the use of frequent intravenous blood glucose sampling and intravenous insulin delivery.[1] Although this system resulted in excellent control of blood glucose between meals and even when challenged with oral glucose loads/meals, it was not a long-term solution because maintaining access to the venous system is difficult due to the possible risk of infection and venous thrombosis (blood clots). The Biostater,[2] a device

Author Affiliation: Sansum Diabetes Research Institute, University of California, Santa Barbara, Chemical Engineering, Santa Barbara, California

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Corresponding Author: Howard Zisser, M.D., Sansum Diabetes Research Institute, 2219 Bath St., Santa Barbara, CA 93105; email address hzisser@sansum.org

incorporating a similar design (intravenous sensing and insulin delivery), is still in use as a research tool performing glucose clamp studies to determine insulin sensitivity in patients with and without diabetes and how medications may alter glucose metabolism.

Current Hurdles to Implementation

The "lag time" between when subcutaneous insulin is delivered and when it actually begins to lower glucose concentration in the blood is one of the rate-limiting factors in the development of an artificial pancreas. The second rate-limiting factor is related to the time delay and inaccuracies in glucose sensing. With current continuous glucose sensors, current insulins, and subcutaneous insulin infusion, this lag time is approximately 75–100 min: 15 min for the sensor plus 60–75 min for the so-called rapid-acting insulin to reach peak effect when delivered under the skin.[3,4] Advanced control algorithms, such as model predictive control, may be able to model some of these delays.

Another complex variable that must be addressed in solving this riddle is the fact that there is significant intrapatient and interpatient variability.[5] It is not as simple as designing a general model of T1DM. There will need to be customization of a general model that will reflect an individual's unique parameters, including insulin sensitivity, insulin-to-carbohydrate ratios (how much insulin to take with meals), correction factors (how much insulin to take to return to a relatively normal glucose), and their response to exercise, illness, alcohol,[6] and travel.

Even though the concept of closed-loop glucose control has been around for a while, it is only with approved devices (continuous glucose monitors and modern insulin pumps) that an artificial pancreas could be considered a viable option and area of research ripe for exploration. Most of the investigations are focused on how to obtain adequate, safe glucose control, i.e., limit glucose concentrations to the quasi-normal range while minimizing hypoglycemia (low blood glucose) and hyperglycemia (high blood glucose). Hypoglycemia can cause acute mental confusion, loss of consciousness, seizure, or even death. Hyperglycemia can cause a life-threatening acidosis in the short-term and can result in long-term vascular complications such as blindness, kidney failure, heart disease, stroke, and amputations.

Possible Solutions

One possible solution that can minimize the current mismatch between rapid absorption of glucose and relatively slow onset of subcutaneously delivered insulin would be to slow down the gastrointestinal tract so that the influx of glucose into the bloodstream coincides with the glucose-lowering action of the insulin. Pramlintide, a synthetic version of the hormone amylin, is one possible way to control the problem more easily. Amylin, first discovered in 1987, is cosecreted with insulin in people without T1DM.[7] Its primary mode of action is to slow down the appearance of glucose in the bloodstream by slowing down gastric emptying and inhibiting secretion of digestive enzymes. Additionally, it inhibits secretion of insulin's counter-regulatory hormone, glucagon, thereby limiting the appearance of new glucose from the liver. Closed-loop clinical studies using pramlintide are currently under review at the Food and Drug Administration and should start shortly.

A second solution would involve designing a way for insulin to start acting faster but also have insulin stop acting when insulin delivery is suspended. One option under investigation is the use of intraperitoneal insulin. With intraperitoneal insulin delivery, insulin takes approximately 15 min to reach peak effect. In an unpublished study, 50% of Tc-99m-labeled insulin delivered into the intraperitoneal space was absorbed in the liver after less than 5 min and 100% after approximately 12 min. This absorption profile effectively changes current fast-acting insulin analogs into ultra-fast-acting insulins. Another significant advantage of intraperitoneal insulin delivery is the reduction in frequency and severity of hypoglycemia as compared with subcutaneous insulin delivery,[8] because there is no depot of insulin continuing to have its effect after insulin delivery is suspended. Intraperitoneal insulin delivery also results in lower levels of circulating plasma insulin with most of the intraperitoneal insulin going directly to the portal circulation.[9–11] Insulin can be delivered into the intraperitoneal space using either an implanted insulin pump[12] or a port in combination with a traditional insulin pump. Risks of peritoneal insulin delivery include infection (mainly skin and pump pocket infections with a much smaller risk of peritonitis) and interruption of insulin delivery due to a catheter issue. Because there is no depot of insulin in patients using intraperitoneal insulin, if there is an interruption of insulin, rapid deterioration in glucose control could occur.

MannKind Corporation (Valencia, CA) is developing the Technosphere® Insulin (TI) Inhalation System for treatment of adult subjects with diabetes mellitus. The TI Inhalation Powder System contains an ultra-rapid-acting insulin whose absorption and exposure times are similar

to that observed in normal physiology. It has the ability to deliver insulin to the deep lung, and with its rapid absorption and unique pharmacokinetic profile, TI inhalation powder mimics early insulin release.[13] The TI inhalation powder's more rapid onset and shorter duration of action may result in both a reduction in postprandial hyperglycemia as well as a decrease in the incidence and severity of hypoglycemia, as compared with commercially available prandial insulins. Technosphere insulin appears in the bloodstream much faster than subcutaneous insulin, mimicking first-phase insulin secretion. Additionally, TI is cleared from the bloodstream faster, resulting in fewer late postprandial hypoglycemic events. Clinical studies are underway using TI in combination with subcutaneous insulin during closed-loop control.

Two new insulin formulations under development may also show promise in this area. ViaJect (Biodel, Danbury, CT) is a novel formulation of regular human (recombinant) insulin that uses a diluent that helps stabilize the monomeric form of insulin in solution. Typically insulin forms a hexamer, which needs to be disassociated into the monomeric form *in vivo* to become active. This allows for a faster onset and offset of insulin action. A second new formulation uses the addition of a spreading agent to get the insulin working faster. Halozyme is a human synthetic version of hyaluronidase that degrades hyaluronic acid, a space-filling, gel-like substance that is a major component of body tissues. It is a naturally occurring enzyme that digests hyaluronic acid to temporarily break down the gel, thereby facilitating the penetration and diffusion of other drugs and fluids that are injected under the skin or in muscle.[14]

Controlling glucose concentrations with insulin is often compared to driving a car using only an accelerator. It can be done, but it is nice to have a brake. Glucagon is the counter-regulatory hormone to insulin. Glucagon increases the blood glucose concentration by facilitating conversion of glycogen to glucose in the liver. Patients with T1DM still make glucagon, but the insulin–glucagon feedback system is disrupted. There are a number of research groups investigating using a dual hormone controller with the idea that glucagon can act as a brake in the event that too much insulin is delivered. This adds another level of complexity to the control problem. One could either choose to have a master controller that delivers either hormone or separate controllers in a bang/bang configuration, which could, in theory, deliver both hormones at the same time. Additional drawbacks include the fact that the current formulation of glucagon is unstable and tends to form amyloid fibrils in solution and that repeated use of glucagon could cause depletion of glucose stores in the liver and would require a dual-chambered pump.

Safety/Monitoring

An area of investigation that has not received much attention is related to long-term safety, risk mitigation, remote monitoring, fault detection,[15] and system maintenance. A fully closed-loop system will need to be able to detect when there is an issue related to insulin delivery (catheter occlusion or unresponsive insulin delivery site) or when a continuous glucose sensor's accuracy begins to fade. A prototype global-positioning-system-equipped continuous glucose monitor has been designed that can alert family and medical staff of the location and glucose concentration (absolute and rate of change) in the event of profound or impending hypoglycemia.[16]

Another area that needs to be explored is redundancy, especially of the continuous glucose monitor. One could conceive of using an array of sensors and voting algorithms to minimize the weakness of any individual sensor or sensing method. Alternative means of sensing glucose will need to be developed. Most of the currently approved sensors use an electrochemical sensor that has an electrode plated with an enzyme that converts glucose to gluconic acid + hydrogen peroxide + two electrons. A secondary sensing electrode counts the electrons and is calibrated periodically to a reference glucose value. A promising new technology is using fluorescent technology coupled to glucose-specific receptors to amplify glucose concentrations and give a precise value.[17] This method appears to have less inaccuracy in the critical hypoglycemic region.

Conclusions

With the discovery and purification of insulin[18] came great hope for individuals with T1DM. While technically not a cure, insulin replacement was a life-saving therapy, halting the previously inevitable downward spiral. One only has to look at before-and-after pictures of the first patients to receive insulin to appreciate the magnitude of this therapy. Through the 1900s, technology has only added additional benefits to patients with T1DM. Measuring glucose concentrations has progressed from crude approximations of urine glucose using powdered chemicals and an open flame to a small electrode placed under the skin, reporting around-the-clock glucose

concentrations. Insulin, once obtained and purified from animals, is now bioengineered to exacting specifications. Insulin delivery devices, once made from glass syringes and large-bore steel needles, now include disposable syringes with microfine needles, insulin pens, and pumps.

We now stand on the cusp of a new era of diabetes research and technology. This and future technology will allow for the development of an artificial pancreas to aid patients in managing their blood glucose control. Most likely, the artificial pancreas will be brought to market in stages.[19] The first stage will probably involve just monitoring the patient. The next systems may then be allowed only to reduce insulin delivery if hypoglycemia is imminent. After that, one could envision overnight closed-loop control because this is a time when there are few disturbances and patients are at greatest risk for severe hypoglycemia. There is a considerable amount of work to be done, but with the development of better sensors and faster insulins, we will be well on our way to getting this technology into the hands of people with T1DM.

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