REVIEW

Type 1 diabetes glycemic management: Insulin therapy, glucose monitoring, and automation

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Despite innovations in insulin therapy since its discovery, most patients living with type 1 diabetes do not achieve sufficient glycemic control to prevent complications, and they experience hypoglycemia, weight gain, and major self-care burden. Promising pharmacological advances in insulin therapy include the refinement of extremely rapid insulin analogs, alternate insulin-delivery routes, liver-selective insulins, add-on drugs that enhance insulin effect, and glucose-responsive insulin molecules. The greatest future impact will come from combining these pharmacological solutions with existing automated insulin delivery methods that integrate insulin pumps and glucose sensors. These systems will use algorithms enhanced by machine learning, supplemented by technologies that include activity monitors and sensors for other key metabolites such as ketones. The future challenges facing clinicians and researchers will be those of access and broad clinical implementation.

Although the specific cause of type 1 diabetes remains unknown, it is generally understood to represent an autoimmune disease marked by the progressive loss of pancreatic insulin-producing β cells, resulting in severe insulin deficiency. The discovery of insulin 100 years ago transformed type 1 diabetes from an imminently lethal disease to a chronic condition. Despite modern advances in treatment, people living with type 1 diabetes today still face an unacceptably high risk of acute and chronic complications and an estimated 10-year loss of life expectancy depending on nationality and age of diagnosis (*1*). The acute metabolic complications of diabetic ketoacidosis, a result of severe relative insulin deficiency, and severe hypoglycemia, a result of relative insulin excess, still affect ~5 and 12 people, respectively, per 100 people annually (*2*). A common misconception is that type 1 diabetes is a disease of youth and type 2 diabetes a disease of aging, as more than half of those with type 1 diabetes have onset in adulthood. The major difference is actually that those with type 1 diabetes typically have an immediate need to initiate complex insulin replacement therapy at diagnosis for survival.

In type 1 diabetes, insulin therapy itself prevents death from diabetic ketoacidosis and can lessen the long-term exposure to hyperglycemia to prevent eye, kidney, nerve, and cardiovascular complications (*3*). Modern insulin therapy, however, is complex. Dose requirements vary widely between people, and they change for individuals over time. Many insulin types exist, with many molecular variations in the structure of human insulin, insulin formulations, and the routes of administration. Though less common, some countries have approved certain add-on–to–insulin drugs typically used in people with type 2 diabetes to help people with type 1 diabetes achieve better glycemic control. Regardless of choice, therapy is guided by glucose monitoring, which may be accomplished by several episodic capillary blood glucose (fingerstick) measures per day or the use of interstitial glucose sensor technology.

Although clear headway has been made in research to restore or replace islets containing insulin-producing β cells as a potential cure (covered in other Reviews in this issue), in this Review, we aim to simplify the complex state of current type 1 diabetes glycemic management with insulin and to present the clinical challenges associated with it and the emerging research that targets these challenges. Finally, we highlight the relevant future research directions in the domains of insulin pharmacotherapy and technological pump and sensor innovations that we feel are likely to have transformational impact on the management of type 1 diabetes in the next 5 to 10 years.

Physiological insulin replacement: The basic principles

Basal insulin

In normal physiology, the islet β cell secretes low-concentration insulin into portal circulation to maintain a stable glucose level during the fasted state. Replacing this basal insulin component over a 24-hour or longer period has represented a particularly difficult pharmacological challenge. After all, it represents the insulin required day to day to allow stable glucose levels, assuming that the person has absolutely no food intake. This basal insulin must therefore enter blood in a stable, reproducible fashion at low-enough levels to prevent hypoglycemia during fasted hours and not suppress lipolysis excessively enough to induce weight gain. At the same time, the dose needs to be high enough to prevent rises in glucose concentration and excess lipolysis and resultant ketone production. In current clinical practice, people with diabetes receive basal replacement in the form of an injected subcutaneous depot of slowly absorbing insulin once or twice per day, or the depot is held in an external mechanical pump that infuses a rapid-absorbing insulin through a subcutaneous catheter at an hourly rate (Table 1 and Fig. 1A) (*4*).

Mealtime and correction insulin

Ingestion of a meal orchestrates a number of stimuli, including the secretion of incretin hormones in the gut that induce rapid increases in insulin levels to maintain stable glucose levels over the course of a meal. This meal-induced insulin secretion generally reaches peak circulating concentration at ~30 to 50 min, returning to basal levels after ~2 to 4 hours (*5*). In those with diabetes, a mealtime dose of a rapid-acting insulin is given by injection or through a pump before starting meals. An additional correction dose of insulin is administered, often as a supplement to mealtime doses, to help reduce blood glucose levels, if elevated, to a prespecified target level. Estimation of the quantity of insulin for these mealtime and correction doses depends on patient profile, glucose levels, and planned meals or exercise, and the decision process is assisted by different patient self-management methods embedded in diabetes education programs that depend on patient choices, education level, and numeracy (Table 1).

The typical insulin regimen consists of a once-daily basal insulin injection and three (or more, if snacks are eaten) combined mealtime and correction injections per day. Insulin is either directly injected or injected through a continuous subcutaneous insulin infusion pump. The typical insulin pump user needs to change the insulin reservoir and subcutaneous catheter every 3 days and manually prompt all of the meal and correction doses of insulin. The effectiveness of these doses for reaching the glucose targets (Box 1) is usually determined by changes in blood glucose concentration over the 4 hours after a meal for carbohydrate ratios; response to a correction dose for hyperglycemia; and, for basal insulin doses, over a fasting period, such as overnight (Table 1).

The fundamental challenges associated with contemporary glycemic management

Insulin replacement therapy is associated with major challenges (Table 1, final section) (*6*–*8*). Successful glycemic management requires a person's active engagement with a diabetes clinical care team made up of a physician, nurse educator, dietician, pharmacist, and frequently also a kinesiologist and a psychologist or mental health specialist. This team helps support people with type 1 diabetes to jointly develop personalized goals, which they then seek to achieve while working to lessen the high

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levels of self-care burden. In addition to clinical burdens, the pharmacological properties of subcutaneous insulin delivery by injection or pump present multiple challenges, including—among others listed in Table 1—hypoglycemia, weight gain, and rising drug and device costs (*6*–*8*). Unfortunately, with the current limitations in these treatment options, it is estimated that as few as one in five individuals in the United States have achieved target glucose levels in this past decade, more than half have become overweight or developed obesity, and many have an excessive fear of developing hypoglycemic episodes (*8*). Though major headway in addressing and decreasing the magnitude of these challenges has been made over the past 100 years, the remaining challenges are at least in part because of deficiencies in the pharmacological properties of insulin.

Innovations in insulin molecular composition, formulation, and delivery

In normal physiology, insulin is secreted by the pancreatic islet β cell in a hexameric conformation—six individual molecules bound to a central zinc molecule—that dissociates rapidly in the portal circulation and targets the liver as its primary site of action, suppressing liver gluconeogenesis and glycogenolysis. The key pharmacokinetic and pharmacodynamic deficiencies with exogenous insulin are the slow absorption from the subcutaneous space into circulation and the delay in transfer from the peripheral to the portal circulation to access the primary hepatic site of action. The result is a delayed effect. For example, an accurate subcutaneous mealtime dose of insulin is still associated with at least a temporary rise in glucose level, and a correction dose requires 2 to 4 hours to judge whether the dose was sufficient. Analogs of the human insulin molecule, which represent variations in the structure of the human insulin molecule to optimize it for delivery into the subcutaneous space, were developed to alter these absorption characteristics to better meet the requirements of basal, mealtime, and correction doses of insulin (*9*).

Strategies to slow and stabilize insulin absorption and action for basal insulin replacement

Until the 1990s, the main strategy to prolong the subcutaneous absorption and action of human insulin was crystallization through protamine enrichment (*10*). Protamine promotes the aggregation of insulin in solution that, on injection, allows gradual dissociation and absorption into circulation. However, this mechanism of protraction is limited by the need for insulin resuspension before injection, insufficient duration of action requiring twice-daily injection, and a high degree of dose-to-dose variability of absorption from the injection site leading to the risk of unexpected, often overnight, hypoglycemia. The first-generation clinically available basal insulin analogs, including insulin glargine (introduced in 2000) and insulin detemir (introduced in 2004) revolutionized basal replacement. More-stable absorption kinetics helped to prevent hypoglycemic episodes, and they provided greater likelihood of achieving 24-hour duration allowing for once-daily dosing for most patients. For glargine,

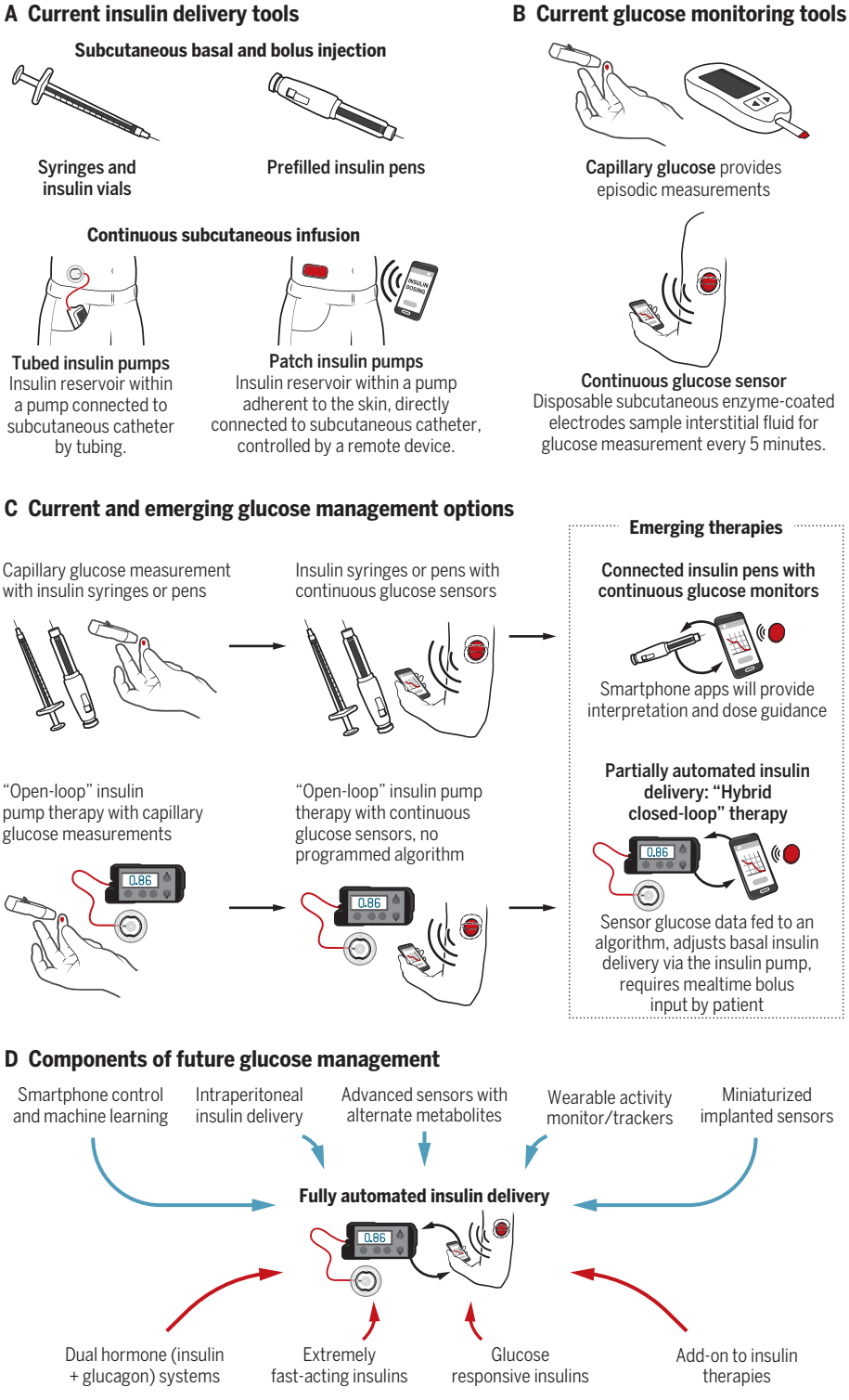

Fig. 1. The pathway to fully automated insulin delivery. (**A** to **D**) Current insulin delivery tools (A) and glucose measurement tools (B) have been adapted into glucose management options that are available or are emerging in practice (C), including partially automated basal insulin delivery. Fully automated insulin delivery that will not rely on the user to manually prompt mealtime insulin doses and will adapt to conditions such as physical activity will require multiple components (D). In (D), blue arrows indicate technological advances, and red arrows indicate pharmacological advances.

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this protraction is induced by alterations in the molecular structure, which lead to a shift in the isoelectric point that induces insulin solubility at acid pH (in the vial) and precipitation of more stable hexamers at the neutral pH found in the subcutaneous tissue (*9*). Detemir's protraction is primarily attributed to the addition of a 14-carbon myristoyl fatty acid to the insulin B–chain, leading to the formation of insulin dihexamers and additional binding of the insulin to tissue and blood proteins, such as albumin. This binding likely contributes to the reduced dose-to-dose variability of detemir, and the resulting lower peripheral circulation bioavailability may also partially explain the attenuation of weight gain observed in its trials. Second-generation basal analog insulins include the hyperconcentration of insulin glargine that serves to decrease the absorption area in the injected depot of insulin to lessen absorption variability and prolong duration. Another second-generation basal analog, insulin degludec, accomplishes the same benefits through the addition of a free fatty acid by means of a linker molecule to minimally modified regular human insulin. It represents the longest-acting and most stable basal insulin in routine clinical use to date, with a half-life of 25 hours and duration exceeding 2 days. By adding a linker molecule and free fatty acid, as well as changes to the excipient solution (fenol), insulin degludec exists as dihexamers in solution but forms long multihexamers when injected in subcutaneous tissue. From these multihexamers, monomers of insulin dissociate very slowly into circulation (*11*). Insulin icodec, currently in clinical trials, is an analog with a bound free fatty acid and linker molecule that further improves the stability to allow once-weekly basal injection (*12*). This has been demonstrated in clinical trials of type 2 diabetes (*12*) but has yet to be studied in the type 1 diabetes population.

Strategies to hasten insulin absorption and action for mealtime and correction insulin

In an effort to avoid subcutaneous injection of insulin, formulations of powdered insulin inhaled by mouth into the lungs were developed and have been commercially available since 2014 in the United States (*13*). This approach has the most rapid absorption into circulation compared with any other strategy studied to date, but it is associated with high production costs, low bioavailability, challenges with precise dosing, dose-to-dose variability in absorption, and concerns about long-term pulmonary safety that have led to the withdrawal of some formulations (*14*). Other strategies to hasten absorption have focused on increasing absorption at subcutaneous injection sites. Examples include devices that heat the injection site to increase blood flow and absorption, the addition of the connective tissue–degrading enzyme hyaluronidase, the use of microneedles to inject into the intradermal space where absorption appears to be more rapid, or other routes such as oral or intraperitoneal absorption.

However, the highest-impact innovations have been accomplished through modification of the insulin molecule to produce rapid-acting, subcutaneously injected insulin analogs (*15*). Three molecules are currently available (aspart, lispro, and glulisine insulin), all of which are characterized by small changes in human insulin peptide structure leading to more-rapid monomer formation and thus more-rapid absorption into circulation from the subcutaneous space. Compared with human insulin injected under the skin, the peak circulating concentration is accelerated by ~1 hour, which allows for injection closer to the time of meals, less meal-induced glucose excursion, and a more-rapid return to premeal glucose levels (*9*). Even more–rapid acting analogs have been introduced into practice (faster-acting insulin aspart and ultrarapid-acting lispro) by altering the solution in which they are administered, leading to an additional acceleration of peak absorption, especially when administered by insulin pump (*16*). In practice, these analogs offer greater flexibility of injection timing before meals without distinct disadvantages over existing alternatives.

Add-on drugs to augment insulin's effect

For people with type 2 diabetes, noninsulin pharmacological therapy has been transformational for improving glycemic control, preventing weight gain, preventing hypoglycemia, and decreasing clinical burden. Although insulin is essential for survival in people with type 1 diabetes because they typically produce very small quantities of or no endogenous insulin, given similar issues of glycemic control, hypoglycemia, weight gain, and burden, many of these add-on drugs used for the management of type 2 diabetes have been explored in the type 1 diabetes population (*17*–*19*). Although the insulin-sensitizing and weight-sparing effects of certain oral type 2 diabetes–specific agents are appealing to consider as adjunct-to-insulin therapies in those with type 1 diabetes who are overweight or obese, metformin and the dipeptidyl peptidase–4 (DPP4) inhibitors failed to demonstrate meaningful glycemic efficacy in trials. Injected incretin analogs, such as glucagon-like peptide-1 (GLP1) receptor agonists, proved efficacious only transiently in improving glycemic control and body weight and seemed to be associated with mildly increased risk of ketosis and hypoglycemia (*17*). The injected islet amyloid polypeptide analog pramlintide—which delays gastric emptying and shares similar trial findings to the GLP1 receptor agonists by primarily improving postprandial glycemic levels—received regulatory approval in the United States for use in type 1 diabetes. However, its clinical uptake has been limited by the burden of three additional mealtime injections per day and excess hypoglycemia during drug initiation as mealtime insulin dose adjustments are needed.

Members of the oral sodium-glucose linked transporter (SGLT) inhibitor class are widely used in type 2 diabetes, where they have shown glucose- and weight-lowering effects and cardiorenal protection beyond their effect on HbA1c (*20*). These agents lower glucose in blood in a β cell–independent manner, owing to induction of glucose excretion into urine. Clinical trials in people with type 1 diabetes have shown meaningful reductions in glycemic levels without increasing hypoglycemia risk, meaningful reduction in weight and blood pressure, and even beneficial effects on markers of kidney disease. However, these drugs are associated with the lowering of insulin doses, a shift in metabolism toward lipolysis owing to the glucose loss in urine, and a stimulation of glucagon secretion that together increase ketone levels and the risk of diabetic ketoacidosis (*21*). Additionally, because of the insulin-independent mechanism of glucose-lowering by urinary excretion of glucose, the glucose concentration during ketoacidosis is often not as markedly elevated as expected by clinicians, which may lead to missed or delayed diagnosis (*21*, *22*). With the expectation that this increased risk can be mitigated to some extent through patient- and caregiver-education, regulatory approvals have been granted in some countries for overweight people with type 1 diabetes under specialist care.

Innovations in technology for glucose measurements and automated insulin delivery

Glucose sensor technology

Understanding a specific patient's glycemic patterns is paramount to diabetes care. Traditionally, this has been achieved with intermittent capillary blood monitoring before mealtime and bedtime but ideally even performed more frequently for optimal self-management and diabetes care team review. However, this does not sufficiently depict within-day or between-day variability that represents the lived experience with diabetes that a continuous measure of glucose can provide. Continuous measurement of glucose concentration has a long history of technological approaches, beginning with intravascular indwelling sensors and the exploration of other fluid compartments, such as sweat, tears, and saliva (*23*, *24*). A transcutaneous interstitial fluid sampling strategy was at one time commercialized as the "GlucoWatch," but acceptance and accuracy was hindered by skin irritation and the diluting effect of sweat. A variety of other technologies have been explored, including microwave and optical sensors—the latter including near-infrared reflectance spectroscopy,

polarized optical rotation, Raman spectroscopy, and fluorescence sensing—as strategies to estimate transcutaneous glucose concentration (*23*, *24*).

The most successful technology to date is the enzyme-based electrochemical approach through direct contact with interstitial fluid (*23*). Early commercialized iterations included microfluidics approaches, but the most accurate advances have been achieved by way of a small, disposable electrode coated with glucose oxidase inserted into the subcutaneous tissue with the help of a retractable needle. The electrode is connected to a transmitter affixed to the skin that sends data to a reader device, smartphone, or an insulin pump for display (Fig. 1, B and C). These sensors are generally placed subcutaneously every 7 to 14 days by the user, although a 6-month completely implanted subcutaneous sensor exists (*24*). Reaction of interstitial fluid glucose with the glucose-oxidase enzyme coated on the electrode generates hydrogen peroxide, which leads to the generation of an electrical current proportional to the concentration of glucose in the interstitial fluid. This current is detected by the system's transmitter and translated into a fairly accurate estimate of blood glucose concentration, originally with the help of calibrations using capillary glucose measurements (*23*). Currently available commercialized devices that use this enzyme-based continuous sensing technology are classified as either continuous glucose monitors that send data continuously to the display device and can trigger, in real time, an alarm for hyper- or hypoglycemia or intermittently scanned glucose monitors that require the user to bring the display device against the transmitter for the data transfer to occur. However, even these latter devices have evolved to include alarms similar to those of continuous glucose monitors, such that this common distinction is less relevant.

Early trials investigating the use of enzyme-based interstitial fluid continuous glucose sensors demonstrated acceptable accuracy for clinical use despite a time lag of 5 to 20 min between the concentration in blood equilibrating with interstitial fluid. These trials demonstrated benefits in blood glucose control and hypoglycemia prevention (*25*). Although adherence to continuous use is challenging, especially in youth, adolescents, and young adults who are less likely to be willing to wear visible devices that declare their diabetes to others (*25*), greater acceptance has been achieved through smaller transmitters, elimination of the need for capillary blood calibrations, improved accuracy, longer duration of wear, regulatory approval to make treatment decisions without a confirmatory capillary blood test (*8*), and improved clinical outcomes (*26*). With the ability to generate 288 or more data points per day, this technology easily surpasses what is feasible with capillary glucose testing and allows for remote monitoring of data and for integration with insulin pumps (Fig. 1, B and C).

Adjusting a pump's basal insulin delivery to maintain glycemic targets

Although the basal insulin coverage by an insulin pump can be delivered independently of glucose levels (termed open-loop pump therapy; Fig. 1C), glucose sensor technology has made possible the moment-to-moment automation of basal insulin delivery by linking communication with the insulin pump (*27*). Early algorithms simply shut off basal infusion temporarily if hypoglycemia occurred or was predicted to occur (*28*), but later improvements led to real-time modification of basal infusion in response to rising as well as dropping glucose levels (Fig. 1C). As basal insulin is automated in these systems but mealtime insulin is not, these systems are referred to as hybrid closed-loop because the user needs to manually prompt mealtime insulin doses. A fully closed-loop, or a fully automated insulin delivery system that includes automation of mealtime insulin, does not yet exist.

Two hybrid closed-loop system approaches have been introduced into clinical practice: a treat-to-range approach, in which an algorithm will adjust preprogrammed basal rates only if predicted to be outside a specific range, and a treat-to-target algorithm that ignores preprogrammed basal rates and constantly determines higher or lower insulin delivery depending on whether current sensor glucose is above or below a specific target. The algorithms use different mathematical models—such as proportional integrative derivative, model predictive

Table 1. Overview of the components of physiological insulin replacement and their clinical challenges.

Basal insulin
Low-concentration circulating insulin to maintain stable blood glucose level during fasting and to suppress excess ketone production (*4*).
Current strategies: NPH insulin injected subcutaneously twice daily, 1st and 2nd generation long-acting insulin analogs, continuous subcutaneous infusion of rapid or ultrarapid analog insulin by open-loop external pump, or sensor glucose-based adjustment of basal delivery in hybrid closed-loop automated insulin delivery systems

Mealtime insulin
Higher-concentration circulating insulin to permit glucose uptake into the liver and peripheral tissues and maintain target blood glucose levels during and after carbohydrate intake (*4*).
Current strategies: Regular human insulin by subcutaneous injection, rapid and ultrarapid analog insulin by injection or by pump, or inhaled insulin (uncommonly used) by one of three methods—fixed dose, estimation range based on patient experience, or a quantitative method using carbohydrate counting and a prescribed carbohydrate-to-insulin ratio.

Correction insulin
Higher-concentration circulating insulin to reduce elevated blood glucose levels to target levels (*4*).
Current strategies: Same insulin types as for food bolus insulin, frequently administered along with the food bolus insulin at times of meals or on its own at bedtime. Doses generally determined by two methods—estimation range based on patient experience or a calculation based on current blood glucose level, the insulin sensitivity factor, target blood sugar level, and an estimation of active insulin remaining from prior boluses.

Add-on therapies to assist insulin's effect
Pharmacotherapies, typically used for type 2 diabetes, added to insulin therapy to help with glycemic control and weight management (*18*, *41*).
Current strategies: Islet amyloid polypeptide analog (pramlinitide, limited to the United States) and SGLT inhibition (limited at present to Europe and Japan).

Clinical challenges with contemporary physiological insulin replacement
High levels of self-care burden (*2*, *6*).
Major physiological challenges: peripheral insulin delivery rather than portal, slow absorption of bolus insulin, and delayed return to basal levels.
Low proportion of patients meet evidence-based glycemic target levels.
Fear of long-term complications.
Fear of hypoglycemia.
Overweight and obesity.
Injection site lipohypertrophy.
Challenges with engaging self-care in children and frail elderly.
Cost of insulin, glucose monitoring, and insulin delivery technologies.

NPH, neutral protamine hagedorn insulin; SGLT, sodium-glucose linked transporter.

control, and fuzzy logic statistical strategies—to achieve these same objectives, and some make day-to-day adjustments in the algorithm parameters to adapt to changing total daily insulin requirements.

In addition to the automation of basal insulin delivery, commercialized systems have introduced automated partial correction doses based on achieved or predicted hyperglycemia (*29*, *30*). These systems moderately reduce glycated hemoglobin A1c and increase time in target glucose range, with the greatest impact in the overnight fasted period (*29*–*31*). Hybrid closed-loop systems can partially address the frequently large day-to-day variation in basal insulin needs, such as the delayed effect of physical activity, ingestion of alcohol, illness, or fatty meals (*32*). However, to date neither this automation nor standard injected basal insulin adequately address acute increases in the demand for basal insulin, such as during the dawn phenomenon (early morning increased insulin demand owing to cyclical counterinsulin hormone secretion), or acute decreases needed immediately during physical activity. Despite these limitations, automation of basal insulin in current hybrid closed-loop systems has represented a major innovation in diabetes care.

Since the approval of the first commercialized hybrid closed-loop system in 2016, many companies have products in development or are seeking regulatory approval (*33*). Given historical delays in the approval of commercialized systems, a do-it-yourself, patient-led movement has developed ways for people with diabetes to connect (or hack) existing commercially available pumps and sensors to open-access algorithms on their smartphones to create their own hybrid closed-loop systems. These systems are not yet approved by regulatory bodies, but observational research has supported their safety and efficacy (*34*). Consequently, collaborations with not-for-profit organizations and industry are expected to lead to their broader acceptance and use.

Future directions and conclusions

Although the search continues for curative therapies, the innovations in insulin molecular composition, formulation, and delivery, as well as the innovations in technologies for glucose sensing and automated insulin delivery, have had profound clinical impact. In these next sections, we review those most likely to have a transformational effect in the next few years. Although each may independently make a major contribution to the management of type 1 diabetes, it is our strong opinion that the combination of approaches centered around improving the functionality of a closed-loop system will have the greatest impact. This fully responsive system will maximize glycemic control while not requiring the burden of announcements for mealtime or physical activity with the help of multiple cointerventions (Fig. 1D).

The future of insulin and add-on pharmacologic agents

The discovery of a subcutaneously injected insulin that is even more–rapidly absorbing than that which is currently available would greatly benefit mealtime control for injected insulin regimens and all forms of insulin pump therapy—potentially even contributing to a fully automated insulin delivery system. An extremely fast-acting insulin, for example, could immediately suppress the glucose rise from a meal rather than requiring the user to prompt the mealtime dose of insulin inherent in current hybrid closed-loop systems. Although the innovations described above to hasten insulin delivery may not succeed in the development of an extremely fast-acting insulin, we highlight the recent discovery of a naturally occurring peptide with human insulin–like bioactivity, derived from the venom of a cone-snail species (*35*). This peptide exists in monomeric form—a key attribute to rapid absorption from the subcutaneous space.

Administration of insulin into the portal rather than the peripheral circulation represents an alternate strategy for a faster onset of insulin action and would additionally lessen overinsulinization of muscle and fat tissue without inherent weight gain risk. In theory, this could be accomplished by the oral delivery of insulin using innovations to aid transfer of insulin across the intestinal barrier into the portal circulation. Unfortunately, issues with consistency of absorption and bioavailability and, in particular, variability of effect will likely prevent its use in type 1 diabetes (*36*). Alternatively, peripheral overinsulinization can be overcome by the mechanical delivery of insulin to the portal circulation through an intraperitoneal catheter (*37*), which has previously been demonstrated to improve glycemic control (*38*). Subcutaneous insulins that could preferentially target the liver have been extensively studied in type 2 diabetes, including development of polyethylene glycol (PEG)–lispro, in which the hydrophobic moiety permits specific entry into fenestrated liver capillaries rather than peripheral tissues. However, metabolic benefit may be hindered by hepatic steatosis, resulting from fatty acid influx owing to the inherent imbalance between peripheral lipolysis and augmented liver insulin signaling.

Finally, we predict that the greatest impact of insulin therapy will be the development of glucose-responsive insulins, developed from resin-based formulations or glucose-binding insulin molecule motifs, which can augment insulin availability to its receptors primarily in the setting of higher glucose concentrations (*39*). Akin to the glucose responsiveness of automated basal insulin delivery using glucose sensor and insulin pump technology, this innately glucose-responsive insulin could have decreased effect during lower glucose levels and augmented effect during hyperglycemia.

In addition to the existing add-on drugs to insulin, somatostatin receptor 2 antagonism aiming to restore endogenous glucagon responses for hypoglycemia prevention are under preclinical research, and adjunctive-to-insulin infusion of glucagon, as well as infusion of pramlintide, are under active investigation in automated insulin delivery system trials (*40*–*43*). Availability of microdoses of subcutaneous glucagon in a dual insulin and glucagon closed-loop pump configuration permits an additional protection from hypoglycemia (*40*), whereas agents like pramlintide and SGLT inhibitors may suppress postprandial glucose rises to permit better algorithm functionality at mealtimes (*41*–*43*).

The future of technologies

Further innovation will be necessary to increase the acceptability of technologies to people with diabetes. Miniaturization of the sensor electrode and its transmitter, development of materials to prolong duration of use of both sensors and insulin infusion sets, and harmonization of sensor and insulin delivery catheter site are key research objectives. Furthermore, measurement of other clinically important metabolites—such as ketone levels that may help to identify insulin infusion set failures or lactate levels for the identification of physical activity—or even the concentration of circulating insulin itself for use in guiding automated insulin delivery systems may be feasible through a number of new technologies (*44*, *45*). Inaccuracies in the quantification of ingested mealtime carbohydrates currently limit the success of hybrid closed-loop systems, as meal-induced glucose

Box 1. The target glycemic levels in type 1 diabetes clinical practice.

Contemporary practice aims for premeal and bedtime targets for most individuals of 70 to 126 mg/dl (3.9 to 7.0 mmol/liter) and postprandial peak levels of 180 mg/dl (10.0 mmol/liter) or below. Thus, in totality, the objective is to spend at least 70% of time in the 70- to 180-mg/dl (3.9 to 10.0 mmol/liter) range as evaluated by continuous glucose sensors. A 14-day consecutive evaluation period with 70% time in range approximately corresponds to a glycated hemoglobin A1c level of 7.0% (*49*)—the target for most adults and children to prevent long-term complications while minimizing hypoglycemia. Although a normal A1c in most nondiabetic adults is <5.7%, and normal glucose concentrations typically range as low as 58 mg/dl (3.2 mmol/liter) fasted and only as high as 144 mg/dl (8.0 mmol/liter) after meals, these higher targets are associated in trials with minimal long-term risk of complications and the potential to reduce hypoglycemia.

variability remains problematic despite the algorithms. One strategy is the development of artificial intelligence applications for smartphones that can help patients estimate carbohydrate content of meals on the basis of real-time photographs of the food. Adaptability of automated insulin delivery systems to physical activity remains problematic, requiring complex and variable strategies to account for exercise that require understanding of the type, duration, and intensity of the exercise. Microboluses of glucagon, as well as integration of wearable devices including activity trackers and galvanized skin thermometers, are under active research in automated insulin delivery systems. Finally, common daily occurrences specific to individual patients, such as hyperglycemia owing to additional snacks or to the dawn phenomenon or hypoglycemia associated with regular physical activity, could preemptively be identified by machine-learning to further inform closed-loop algorithms (*46*).

Although we have focused on presenting a future vision for type 1 diabetes glycemic management in which multiple choices of insulin formulation, insulin delivery, and related add-on drugs as well as technologies could be used independently or in combination to maximally achieve a fully automated closed-loop system (Fig. 1D), we acknowledge three main considerations. First, although we believe that multiple options to choose from will benefit people with type 1 diabetes, we recognize that the components of a fully automated system may further add to the current high cost of therapy, even if counteracted by the prevention of complications, and further amplify existing socioeconomic disparities in clinical access (*47*). Second, many people with diabetes are adverse to wearing devices and will choose injection therapy. Early versions of smartphone-connected insulin pens that offer an alternative to wearing insulin pumps have entered clinical practice, and refinements are expected in the ways that they themselves can be harmonized with glucose sensors and, though not automated, can help guide insulin dosing (Fig. 1C) (*48*). Finally, the use of connected devices offers the opportunity for data sharing with caregivers and health care providers. The international lockdown orders that required limiting in-person health services during the 2020 and 2021 severe acute respiratory syndrome coronavirus 2 pandemic have truly advanced the adoption and development of telehealth technologies and virtual care in type 1 diabetes that may, in the future, represent a critical component of glycemic management support. Until we succeed in curing type 1 diabetes, we envision a future in which the innovations in type 1 diabetes will be integrated with automated machine-learning decision-support tools and in which the complexities of glycemic management will be, at least in part, supported virtually.

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