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Assessment of Risks and Benefits of Beta Cell Replacement Versus Automated Insulin Delivery Systems for Type 1 Diabetes

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Abstract

Purpose of Review Current approaches to insulin replacement in type 1 diabetes are unable to achieve optimal levels of glycemic control without substantial risk of hypoglycemia and substantial burden of self-management. Advances in biology and technology present beta cell replacement and automated insulin delivery as two alternative approaches. Here we discuss current and future prospects for the relative risks and benefits for biological and psychosocial outcomes from the perspective of researchers, clinicians, and persons living with diabetes.

Recent Findings Beta cell replacement using pancreas or islet transplant can achieve insulin independence but requires immunosuppression. Although insulin independence may not be sustained, time in range of 80–90%, minimal glycemic variability and abolition of hypoglycemia is routine after islet transplantation. Clinical trials of potentially unlimited supply of stem cell-derived beta cells are showing promise. Automated insulin delivery (AID) systems can achieve 70–75% time in range, with reduced glycemic variability. Impatient with the pace of commercially available AID, users have developed their own algorithms which appear to be at least equivalent to systems developed within conventional regulatory frameworks. The importance of psychosocial factors and the preferences and values of persons living with diabetes are emerging as key elements on which therapies should be evaluated beyond their impact of biological outcomes.

Summary Biology or technology to deliver glucose dependent insulin secretion is associated with substantial improvements in glycemia and prevention of hypoglycemia while relieving much of the substantial burden of diabetes. Automated insulin delivery, currently, represents a more accessible bridge to a biologic cure that we expect future cellular therapies to deliver.

Keywords Type 1 diabetes · Islet transplant · Automated · Insulin delivery · Closed loop · Hypoglycemia

Background

It is clear that average life expectancy for individuals with type 1 diabetes (T1D) continues to be reduced compared with the general population, and microvascular complications are a major contributor to morbidity and mortality [1]. Even with access to modern insulin analogs, technologies (pumps and sensors) and effective self-management education and support less than 10% achieve recommended glycemic targets [2].

T1D is somewhat unique in the degree to which its day to day management is delegated to the affected individual. The complexity of diabetes self-management may be underestimated and/or under acknowledged by healthcare professionals, whereas it is often highlighted by persons living with diabetes. Typically, healthcare providers emphasize strict glycemic control with the goal of reducing the risk of long-term microvascular and macrovascular complications. For persons living with diabetes however, the short-term risk of

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hypoglycemia is a common barrier to achieving these glycemic goals and the complexity of integrating diabetes self-management into everyday life often exceeds the capacity of affected individuals, resulting in diabetes distress and burnout. It was stated recently that "diabetes is at 'peak burden'" (P Choudhary, personal communication). Adding to the complexity of T1D self-management seems unlikely to be a successful strategy.

Beta-cell replacement and automated insulin delivery (AID) systems however are two broad approaches which have the potential to realize the dual objectives of delivering safe and effective glycemic control while reducing the burden of self-management for persons living with diabetes. Though long-anticipated and having always seemed to be receding into the future, these approaches are becoming clinical realities. In this review, we will seek to describe the current and anticipated benefits and risks of these two alternative approaches. Importantly, we have sought to incorporate the differing perspectives of both healthcare providers and persons living with diabetes while considering the risks and benefits of these novel approaches to therapy.

Limitations of Current Insulin Delivery for T1D

It is all but impossible to accurately replicate the closely regulated euglycemia achieved by glucose-dependent, intraportal insulin delivery from a healthy pancreas in the face of fasting or feasting, exercise, growth and development, and other physiologic challenges as a result of a complex integration of nutrient, endocrine, paracrine, and neural signals. Mismatches between insulin needs and availability following systemic delivery of insulin by subcutaneous injection or infusion, or by inhalation, are common resulting in glycemic variability manifest as both hypo- and hyperglycemia [3]. As a result, recommendations to target near-normoglycemia (where it can be achieved safely) to reduce (but not eliminate) the risk of development or progression of microvascular complications are extremely hard to achieve.

Healthcare practitioners are well aware of sub-optimal glycemic control (usually measured by HbA1c), hypoglycemia, and weight gain as limitations of current available therapies. There is also growing awareness of the complex interplay between T1D, psychosocial factors, and mental health. Current diabetes management is burdensome; it requires numeracy, literacy, and significant cognitive abilities and problem-solving skills. Diabetes distress, though common [4], may be overlooked as the cost of doing business.

The unpredictability of blood glucose levels is a major frustration for persons living with diabetes, while most diabetes education implies a logic and predictability; this is not reflective of the lived experience for many affected individuals. Short of a "cure," for many affected individuals, predictable blood glucose levels (resulting in less anxiety and worry) would represent a meaningful improvement for life with diabetes.

Approaches to Beta Cell Replacement

Islet and Pancreas Transplantation

The intraportal infusion of islets isolated from deceased organ donors has become established as a clinical therapy in some parts of the world since the publication of the Edmonton protocol 20 years ago [5]. This built on the approach of autotransplantation of islets in individuals undergoing total pancreatectomy to avoid (or ameliorate) the brittle diabetes which would otherwise result. Transplantation of the whole pancreas (requiring major abdominal surgery) is an option for select individuals with T1D (particularly those requiring simultaneous kidney transplant) [6]. The limited availability of donor organs for transplant is well known and would never be sufficient to treat more than a small fraction of persons with T1D. This has prompted the search for alternative, potentially unlimited, sources of beta cells.

Stem Cell-Derived Beta Cells

Clinical trials of encapsulated pancreatic progenitor cells derived from human embryonic stem cells which began in 2014 are ongoing. Initial approaches demonstrated effective immune isolation, but very low cell viability because of inadequate vascularization. Subsequently, perforated devices, combined with systemic immunosuppression, have been tested. Recent press releases reporting the detection of C-peptide suggests the presence of functional beta cells [7]. Substantial milestones remain before encapsulated stem cells can be applied routinely in clinical practice [8•].

Immunologic Considerations

Protection of replacement beta cells from immune attack is a fundamental issue. Controlling the immune system with chronic immunosuppression (until immune tolerance becomes possible) is effective in islet transplantation. Using encapsulated cells could avoid chronic immunosuppression but has not yet been demonstrated successfully in humans. A unique issue in persons with T1D (in addition to alloimmunity) is recurrent beta cell autoimmunity which may be a challenge for all beta cell sources—even for a beta-cell replacement product derived from autologous (the patient's own) induced pluripotential stem cells.

Benefits of Beta Cell Replacement

With the engraftment of sufficient islet mass, insulin independence can be routinely achieved in islet allotransplantation. Maintaining long-term (e.g., > 10 years) insulin independence has proven more difficult, although it has been observed in a small number of cases [9, 10] (and personal observations). Protection from severe hypoglycemia however is much more durable (maintained for more than 10 years in 80% of subjects) as long as some islet function persists [11].

The benefits of islet transplantation seem to be directly related to beta cell reserve. Detailed metabolic studies have shown that insulin-independent islet transplant recipients generally have a lower islet mass than healthy control subjects [12]. Studies using continuous glucose monitoring (CGM) have shown that higher levels of islet function are required to maintain euglycemia; lower levels of islet function are however sufficient to reduce glucose variability, while minimal levels of islet function are required to protect from hypoglycemia [13•].

Thus, even if some patients will eventually need to restart insulin therapy, the benefits of even small amounts of endogenous, glucose-dependent insulin secretion (measured as residual C-peptide production) should not be underestimated. Indeed a small fraction of patients living with T1D demonstrate persistence of C-peptide, and these patients are less exposed to hypoglycemia and present with lower glucose variability [14] as well as fewer microvascular complications compared with patients without measurable C-peptide [15, 16]. It may not be possible for beta cell replacement to reverse established diabetes chronic complications, although clinical observations suggest a generally positive effect of islet transplant [17, 18] although some immunosuppressant drugs are nephrotoxic.

Protection from severe hypoglycemia (which is currently the main indication for islet transplantation) is clinically important. Reduced glucose variability and hypoglycemia should be associated with restoration of hypoglycemia awareness [19, 20] but would also address elements which are important and key contributors to diabetes distress.

Risks of Beta Cell Replacement

The procedure of intraportal infusion of islets is minimally invasive with small risks of bleeding and/or portal vein thrombosis which can be mitigated [21]. The major risks of current approaches to beta cell replacement (i.e., islet allotransplantation) are those resulting from the need for lifelong immunosuppression particularly increased risk of infections and neoplasia. The risks of opportunistic infections can be minimized by appropriate prophylaxis for transmission or infections with cytomegalovirus, Epstein-Barr virus and *Pneumocystis jirovecii*, and close clinical follow-up. Squamous and basal cell skin cancers are a common but manageable complication of long-term immunosuppression requiring regular surveillance. Post-transplant lymphoproliferative disease has been reported after islet transplantation [22] with rates similar to other organ transplants (approx. 1%). It seems reasonable to assume that higher risks of cancer seen in solid organ transplant recipients should be expected in islet transplant recipients taking chronic immunosuppression. Nephrotoxicity is an important consideration for persons with T1D, and current calcineurin inhibitor-based regimens may be problematic for individuals with limited renal reserve.

It is too early to accurately assess the risks of alternative sources of beta cells. Macro-encapsulation approaches, if successful, could avoid the need for immunosuppression, while sub-cutaneous implantation could avoid risks for portal vein thrombosis. The systemic delivery of insulin may not be a substantial disadvantage (since whole pancreas transplants can be successful regardless of their venous drainage). Encapsulation to prevent migration and to permit removal of cells has also addressed concerns around the potential for unrestricted growth of stem cell-derived cells used for beta cell replacement (causing teratomas or other neoplasia). Xenotransplantation is recognized to carry additional risks of zoonoses.

Approaches to Automated Insulin Delivery (AID)

Both commercial organizations (developing devices and/or algorithms) and academic groups (developing and testing algorithms) have been active in this field. The general approach underlying AID is to replicate the stimulus-secretion coupling seen in beta cells using technology to couple insulin delivery with blood glucose levels. A closed-loop system is designed to use an algorithm to dynamically adjust insulin pump delivery based on values from a continuous glucose monitor (CGM). First generation products integrating glucose sensing and insulin pumps suspended insulin delivery when hypoglycemia was detected (or anticipated) to reduce duration and frequency of hypoglycemia. Second generation products mitigate both hypo- and hyperglycemia, but users are still required to adjust their therapies for meal announcement and physical activity. While hybrid closed-loop devices are available in several countries, no fully closed loop AID systems are commercially available yet. A proposed road map has helped guide progress to bringing automated insulin delivery to the clinic (Kowalski).

Perceiving the multiple benefits of the closed loop approach, frustrated by the length of development and regulatory approval as well as potential major cost of commercial closed-loop AID device, the communities of persons living with or affected by T1D have developed and share DIY (do-it-

yourself) solutions to integrate existing insulin pumps and glucose sensors to build their own closed-loop AID systems. Attitudes toward this third community seem to have shifted somewhat recently, with presentations at diabetes conferences and an announcement of willingness of industry to partner with the DIY community (Tidepool Loop https://www.tidepool.org/loop). Conversely the FDA recently issued a warning against "using unauthorized devices for diabetes management used alone or along with authorized devices" [23], while a cease and desist for reverse engineering the LibreLink app was issued by lawyers acting for Abbott [24] The requirement for commercial solutions to meet regulatory standards is an obvious factor explaining the relatively limited features of currently marketed products.

Required Components of Automated Insulin Delivery System

Continuous Glucose Monitoring

The development of accurate continuous glucose monitoring devices has been a critical step toward developing this technology. Currently the most widely used glucose sensing uses glucose oxidase to measure glucose concentrations with a transcutaneous probe in interstitial fluid which reflects blood glucose levels (albeit at much lower concentrations and with a significant temporal delay). Previous requirements for calibration to blood glucose levels have been overcome for most devices, but limited sensor life continues to be a challenge with a current maximum of 14 days. The effectiveness of some implantable glucose sensors for 6 months is being tested (NCT03808376) with a recent announcement that the trial will be extended to 12 months [25]. Other noninvasive approaches to CGM continue to be investigated.

Insulin Delivery Systems

Although implantable insulin pumps delivering insulin into the peritoneal cavity were first demonstrated [26], most AID systems have focused on external insulin pumps delivering insulin subcutaneously. Thus, reliability of these pumps to deliver insulin consistently is a key factor for the success of AID. The interruption of insulin delivery as a result of occlusion or displacement of infusion sets is a common challenge. Modern insulin analogs seem less likely to crystalize (causing occlusions), and have more rapid onset when delivered subcutaneously, compared with recombinant human insulin [27]. Some AID systems under development incorporate both insulin and glucagon—analogous to driving with an accelerator and a brake—which further decrease hypoglycemic risk while potentially targeting a lower glucose levels, albeit with increased complexity and costs [28]. Alternate approaches using other hormones such as pramlintide are also under investigation. It is possible to speculate that insulin with improved pharmacodynamics with both more rapid onset and shorter duration might obviate this perceived need for glucagon.

Algorithms and Control Systems

While maintaining stable glucose levels during fasting is relatively easy, doing so during or after physical activity or meals is more challenging [29, 30]. Algorithms have been developed which automatically adjusts the insulin infusion rate based on sensor data to keep glucose values in a specified target range. The simplest algorithms are proportional integral derivative (PID) controllers where insulin infusion rates are adjusted depending on how far sensor glucose values are from target (proportion), for how long this persists (integral), and what the current rate of change is (derivative). PID controllers are thus reactive and can be slow to adjust when faced with large changes, with the potential to overshoot.

More advanced algorithms used model predictive control which is more suited to dynamic situations. Rather than merely reacting to glucose values, these algorithms can make adjustments to the insulin infusion rate based on their prediction of future state. These algorithms use a model of the effects of insulin and meals on glucose levels (e.g., typical basal rates, insulin sensitivity, insulin-carb ratio, duration of insulin action) and will calculate required adjustments based on sensor data, glucose targets, and limits imposed on the model (e.g., no increase > 100% of the basal rate).

Further advances are models employing fuzzy logic which are better equipped to deal with complex, nonlinear biological systems that are difficult to model, and allow for multiple inputs and multiple outputs (e.g., [31]). The application of machine learning and artificial intelligence may permit even more advanced algorithms in the future which can adapt and learn.

The algorithms may run on a stand-alone computer, such as a cell-phone, or be incorporated into the insulin pump itself. In general, wireless technology (Bluetooth or radio frequency) is used for communication between devices. Individual preferences for modular systems (where components could be updated, but may have inter-operability issues) versus all-in-one systems (where elements have been designed to work together harmoniously) will persist until common standards are agreed upon.

Benefits of Automated Insulin Delivery

Evidence for benefit from AID systems is predominantly derived from short-term clinical trials. For DIY systems, data is more limited, and generally observational without systematic reporting of side effects. The majority of users are early

adopters who have chosen to use this technology. Randomized designs are unusual, although some studies have employed a cross-over design. Trials have generally excluded subjects at high risk for severe hypoglycemia.

A recent meta-analysis of out-patient clinical trials has shown that AID systems significantly increase the amount of time in target range (4.0 to 10.0 mmol/L) from 58 to 70% (an increase of 2.5 h per day) and significantly reduced the time spent in hypoglycemia (< 4.0 mmol/L) by 35 min per day [32••]. Overnight control was superior to 24-h control, and trials using dual hormone systems had greater advantages (larger increases time in range 19% vs 11% and clearer reductions in hypoglycemia) than in single hormone studies—although the comparator arms were different. (Single hormone studies had sensor-augmented pumps as the comparator—which are known to reduce time spent in hypoglycemia; while dual hormone systems were compared with pumps with blinded CGM.). Similar data were seen in another meta-analysis which also observed a 0.26% reduction in HbA1c [33].

Initial self-reports of increased time in range, lower HbA1c without severe hypoglycemia from the DIY community [34], have been confirmed and extended. Observational data from individuals moving from sensor-augmented pumps to an AID system (OpenAPS) have shown improvements in glycemia (of similar magnitude to those observed in clinical trials) in terms of increased time in range (4–10 mmol/L: 80 vs 71%), less time below 3.0 mmol/L (0.9 vs 1.6%), lower mean glucose, estimated A1c, and glycemic variability (glucose CV) [35•].

Patient reported, and psychosocial, outcomes have been relatively under-explored, although this is changing. An earlier review found that only 4 out of 103 active clinical trials were measuring psychosocial factors [36]. A more recent review indicates that user experience with AID is generally positive highlighting common themes of reduced anxiety, improved sleep, and lower cognitive burden from diabetes [37]. The ability to trust the AID systems is a key factor which seems to increase over time, and greater use of AID seems to be associated with larger benefits [38], although the direction of this association is not clear. Pre-existing attitudes to technology also appear to have a significant impact on perceived benefits [39]. Satisfaction with current diabetes treatment may also affect the ability of AID systems to affect this outcome.

Overall, it seems that the psychosocial impacts of AID are complex; they may diverge from biological outcomes and will be highly variable depending on the personality, preferences, and engagement of users, while their context (e.g., family and social support, attitudes of healthcare professionals) adds further complexity [37]. These systems also imply a profound reshaping of interactions between healthcare professionals and users which have often been occupied by discussions around adjustments of insulin doses—potentially creating time to address other aspects of care.

Risks of Automated Insulin Delivery

For individuals who are risk averse (which includes most diabetes care professionals), it may be instinctive to overestimate the risks of novel therapies. It is important to consider those risks which arise over and above the risks inherent in self-management of T1D, or the use of conventional therapies. Many of the risks of AID systems are in fact related to those of the individual components (pump failure, infusion set problems, sensor errors) which may form part of conventional treatments used by persons with T1D. The delivery of excess or insufficient insulin causing severe hypo- or hyperglycemia or ketoacidosis as a result of control algorithm or miscommunication between devices would clearly be an adverse effect of the AID system.

Clinical trials are designed to minimize risk to participants and could underestimate risks in real world. Conversely, clinical trials of early prototypes may be at higher risk of failure. One meta-analysis reports low rates of severe hypoglycemia (6 cases with AID and 3 cases with control treatment among 804 participants in 27 studies), but did not examine risk for diabetic ketoacidosis [33]. Some episodes of severe hypoglycemia and of DKA have been reported in some longer studies (12 weeks) reported more recently. One study reported 1 episode of DKA (8.7/100 patient years) in the closed loop arm (versus 0 in the control arm) and 2 episodes of severe hypoglycemia in each arm (17.4 and 20.3/100 patient years, respectively) [40]. Nine episodes of severe hyperglycemia and 5 episodes of severe hypoglycemia during closed loop treatment (versus only 3 episodes of severe hypoglycemia in the control period) and no cases of ketoacidosis were reported in a "real-life" crossover trial in 68 adults [41]. None of these adverse events were due to the algorithm, with all of the hyperglycemic events attributed to pump and/or infusion set problems. The severe hypoglycemic events were attributed to excessive bolus delivered by the user (over-ride system recommendation; $n = 1$), miscommunication between devices ($n = 1$), and concerningly, pump malfunction in 3 cases.

With the advent of SGLT2 blocking drugs and renewed interest in restriction of carbohydrate intake, it may be important to recognize the limitations of AID systems which rely on sensor glucose values to determine insulin doses. We have observed a case of euglycemic DKA in an individual using Loop in this context (i.e., combined with low-carbohydrate intake and SGLT2 blocker). Some have proposed integration of a ketone sensor into AID systems as a means to enhance safety [42].

While broadly positive, patient reported outcomes have highlighted some negative issues around ability to trust the technology and new burdens. Common burdens reported in published literature include frustrations with the operation of the technology, the size or bulk of the equipment, intrusive alarms, and increased time devoted to thinking about diabetes [37]. These may be system dependent, and diminish over time (as technologies mature and as users become more familiar

with their tool). For some people, the dislike of being attached to a device or the challenges to body image, sense of self, or sense of stigma can be significant barriers to the use of many technologies in diabetes. Some users have faced difficulties with adhesives (for sensors or infusion sets) not proving effective or causing contact dermatitis.

Access to diabetes technologies is limited in many parts of the world. Insurance coverage for CGM lags behind that for insulin pumps in many parts of the world. OpenAPS software is only compatible with older (discontinued) insulin pumps resulting in challenges sourcing functional, and reliable, units. Loop can also be used with OmniPod devices. We have alluded to limited access to self-management education and support for T1D in general, but this is even more acute for persons using DIY closed-loop systems—who primarily rely on the user community for support and guidance. Lack of knowledge and the uncertainty around the status of unapproved technologies among healthcare providers are likely important contributing factors.

Which Is the Better Choice?

It seems that both beta cell replacement and automated insulin delivery systems have similar overarching aims—to deliver insulin in a glucose-dependent fashion while reducing the burden of diabetes (an overview is provided in Fig. 1). It seems that both approaches can have substantial and positive impacts on clinically important biological (glycemic) parameters. Both approaches are associated with psychosocial outcomes which are viewed as positive, but with some cost in terms of burden or worry [37]. Farrington helpfully highlights the impact of beliefs and attitudes toward technology on perceptions of its benefits, which parallels our experience of the importance of exploring the goals and expectations of individuals seeking islet transplantation [43].

With novel therapies, there are insufficient data to precisely assess the magnitude of risks and benefits, particularly over the longer term. While data describing risks is required to inform choices, individuals will interpret these data very differently, and multiple other factors will affect decisions. As clinicians working in islet transplantation, we seek to provide persons with diabetes a unique, individualized assessment of the likely risks and benefits of islet transplantation in order that each individual can be helped to make a decision which aligns with their beliefs and values and that neither overestimates the risks nor the benefits. We provide a summary of the relative benefits of AID or beta cell replacement versus conventional therapy in Table 1.

In our experience, many persons with T1D are better able to accept uncertainty than healthcare professionals. This may

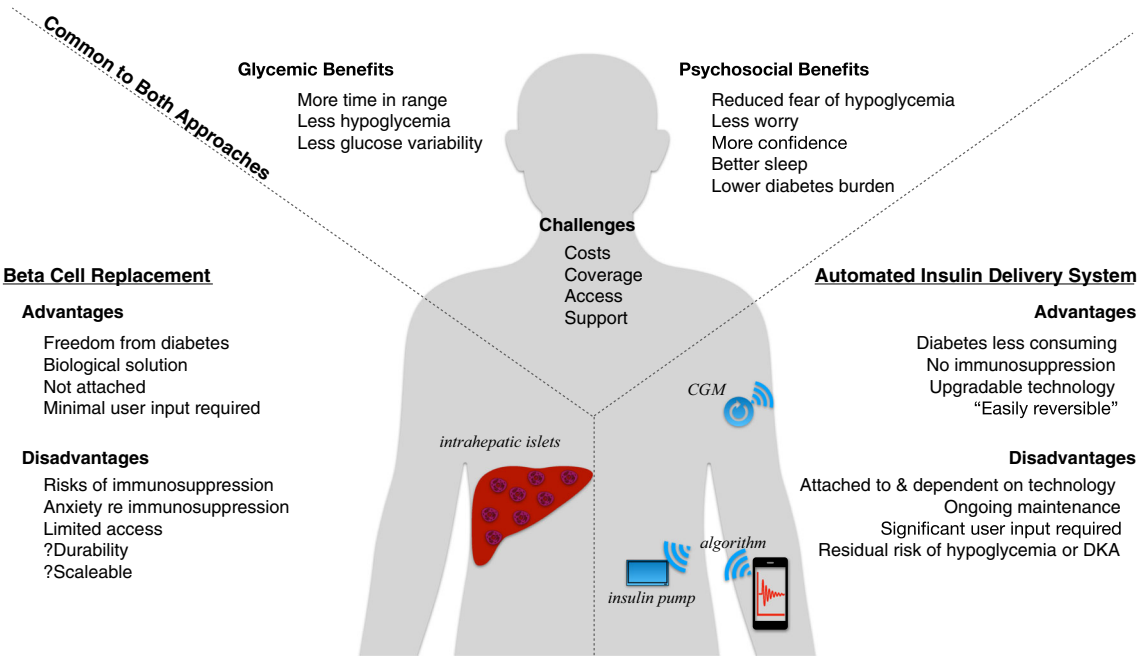

Fig. 1 Illustration of the advantages and disadvantages of current approaches to automated insulin delivery and beta cell replacement. Future developments and enhancements may address some of these disadvantages and/or limitations. User input for islet transplantation is merely to ensure adequate intake immunosuppressant drugs (tablets dosed once or twice daily). For artificial insulin delivery systems, user input includes regular filling pump with insulin, infusion set and site changes, sensor insertion (± calibration), estimation of carb content of meals, and announcing meals and exercise. Because of the potential for interruption or inappropriate insulin delivery of insulin, there is a residual risk of hyper- and hypoglycemic emergencies with artificial insulin delivery systems. Severe hyperglycemia and/or DKA could arise if there was acute loss of replacement beta cells

Table 1 Comparison of relative benefits and demands of automated insulin delivery systems or beta cell replacement in comparison with conventional therapy for type 1 diabetes

	Type 1 diabetes*	Automated insulin delivery	Beta cell replacement
Glycemia			
Time in range	High to low	High	Very high
Glycemic variability	Low-high	low	Very low
Risk for hypoglycemia	+ to +++	0/+	0
Workload			
User input	+++	+	0
User maintenance	+ to ++	++	minimal
Watchfulness required	+ to +++	+ to ++	minimal
Psychosocial			
Cognitive burden	+ to +++	0 to +	0
Anxiety/distress	+ to +++	Variable^	Variable^

*Values in this column reflect estimates of relative benefits and demands encountered by persons living with diabetes striving to maintain moderate glycemic control. ^Generally low in individuals who have selected to choose and/or continue these therapeutic approaches

be manifest as a false dichotomy—either stay with conventional therapy or move forward with AID systems or beta cell replacement. It may represent a failure to explore the individual's degree of dissatisfaction and/or distress with conventional therapy. If the AID system is not of sufficient value or the islet transplant stops working, individuals can revert to their previous treatment or explore the other approach. Thus, the decision should perhaps be framed as an individualized choice from a range of options and acknowledge uncertainty, rather than as a guaranteed therapy recommended by an omniscient expert. Use of the principles of shared decision-making would thus be appropriate [44].

AID Is a Bridge to Future Cellular Replacement Therapies

It seems premature to judge whether AID or beta cell replacement is the better treatment—particularly in the absence of any direct comparative studies. The practicalities of limited access (to technology or viable beta cell replacements) and complex, varied psychosocial factors (which are not easily measured), are likely to dominate decision-making over any perceived advantages in biological parameters (Table 2).

Time in range, time in hypoglycemia and glucose variability in published reports suggest that islet transplantation is superior to AID systems tested to date, even in the absence of insulin independence (Table 3). Given the primacy of safety in clinical trial design, it may be possible to increase time in range with more aggressive algorithms (but this might be at the expense of greater hypoglycemia). Nevertheless, the results of islet transplantation are impressive considering the high-risk population selected for transplant (frequent, severe hypoglycemia and/or extreme glucose variability). AID is progressing rapidly with increased accuracy of CGM and more compact devices.

Conclusions

After decades where glycemic control seemed static and advances in therapy for T1D seemed to increase the burden for affected individuals, it appears that therapies which can improve biological and psychosocial outcomes while reducing the burden of diabetes are tantalizingly close. There is still substantial scope for further innovation and refinement in these innovative therapies if they are to be effectively and safely applied in routine clinical practice. Substantial work

Table 2 Simplified choice matrix illustrating the potential interplay between attitudes to technology and diabetes management which might lead to different preferences for novel therapeutic approaches

	Hands on approach to diabetes/need for control	Hands off approach to diabetes
Trust technology	AID system	?
Technology averse	?	Beta cell replacement

There are clearly multitude of other factors which will contribute to individual preferences, not least in terms of perceptions of risks, attitudes, values, beliefs, personality and experiences

Table 3 Glycemic parameters reported for Beta Cell Replacement and Automated Insulin Delivery systems compared with conventional therapy in T1D

	Time in range (3.9–10 mmol/L)	Time low < 3.9 (or < 3.0) mmol/L	Glucose CV (%)	Comments/ref
Conventional therapy				
T1 CSII + CBGM	67.9%	3.5%	35.8%	HbA1c < 8.5%. No severe hypoglycemia (0.56 u/kg/day) [45]
High-risk T1D	59% *	*(^6.8%)*	44.3%	(Frequent, severe hypoglycemia on islet transplant wait list) [45]
Meta-analysis of APS trials				
APS in clinical trials	74%	2.43%	Not reported	Meta-analysis [32••]
Commercially available APS				
Medtronic 670G	73.8%	3.4%	30.3%	Adult subgroup [46]
Tandem control IQ	71%	1.58 *(^0.9)*%	not reported	6 months trial [47]
DIY/OpenAPS				
OpenAPS	80.4%	4.2 *(^0.9)*%	34.5%	After switching from sensor-augmented pump to OpenAPS [35•]
Beta-cell replacement				
Islet transplant—insulin free	91%	0.3%	20.9%	0 u/kg/day [48]
Islet transplant using insulin	81.8%	0.2%	26.5%	insulin 0.1 to 0.33 u/kg/day [48]

*3–10 mmol/L; ^< 3.0 mmol/L. It has been suggested that the targets for glucose CV should be < 30%, time in range > 70% (with > 90% being ideal) in beta cell replacement (IGLS), while glucose CV above 36% have been deemed unstable by an International consensus group [49]

to develop true partnerships between healthcare providers, persons living with diabetes, academics, industry, and regulators is required to achieve rapid and successful clinical translation. There is more than enough room for both beta cell replacement and technology-based strategies, and it would be a mistake to forget about the wide range of unique personalities, the shifting needs over a lifetime, and the importance of individuals' ability to choose. We believe that beta cell replacement will become the treatment that most persons with diabetes will want, but in the meantime, AID technology is an exciting tool to improve lives and reduce the burden of diabetes.

Compliance with Ethical Standards

Conflict of Interest PAS and AL are supported by the Alberta Academic Medicine and Health Services Plan, are attending physicians in Alberta Health Services Clinical Islet Transplant Program, and co-investigators in Clinical Trials of Viacyte's pancreatic progenitors. KF is a lived experience subject matter expert (Patient-Partner) and founder of Looped—a Facebook group for people using DIY AID. PS, KF, BP, and RRL are investigators in Diabetes Action Canada—a patient-oriented research network supported by CIHR.

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- •• Of major importance

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