Closed-loop systems: a bridge to cell therapy for type 1 diabetes?

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Despite considerable advances in treatments and technologies for people with type 1 diabetes, the treatment framework has remained largely unchanged since insulin was discovered 100 years ago. While many innovations have delivered modest gains in reaching glycaemic targets and reducing diabetes-related complications, they often come with increased complexity and burden, and hypoglycaemia remains a serious issue. The emergence of automated insulin delivery (AID) systems have the potential to allow the achievement of optimal glycaemic targets with less burden, but in our view, it is not the ultimate solution.

Key studies, randomised controlled trials, and real-world data show that automated insulin delivery systems help attain glycaemic targets and improve quality of life, and might reduce diabetes-related distress.[1] Recent independent cost-effectiveness appraisals in high-income countries recommend their use at a population-wide level for most people with type 1 diabetes.[2] However, a recent analysis of registry data from the USA showed that even with high uptake rates of diabetes technology, over 35% of people do not meet recommended HbA_{1c} targets, and 4·7% have recurrent severe hypoglycaemia.[3] These data show a substantial residual risk for both acute and chronic complications. Furthermore, device burden and adverse effects on psychological wellbeing might offset improvements. Diabetes devices can also be associated with serious adverse events.[4]

Further advances are anticipated with more user-friendly devices, fully closed-loop and bi-hormonal systems, and improved algorithms benefiting from artificial intelligence and machine learning. Nevertheless, these advancements will still face limitations in replicating true physiology due to the pharmacokinetics of subcutaneous insulin administration, requirements for and lag time from continuous glucose monitor derived glucose levels, device attachment, and day-to-day technology burden for the user. Using automated insulin delivery systems also requires some level of digital literacy and training for users, caregivers, and health-care professionals. Ultimately, people will still have diabetes.

β-cell replacement to provide endogenous, glucose-dependent insulin secretion is an alternative approach. The finite number of organ donors and the need for lifelong immunosuppression limits the availability of pancreas or islet transplantation to only a small number of people with type 1 diabetes. Currently, β-cell replacement is reserved for those with recurrent hypoglycaemia or requiring a renal transplant, as an alternative to pancreas transplantation.

The potential for cell therapy has been established by islet cell transplantation, which is minimally invasive and has fewer risks compared with pancreas transplantation.[5] A 20-year follow-up of islet transplant recipients showed patient survival rates of 90% and graft survival rates of 48%.[5] Although the median duration of insulin independence was 3 years, it was sustained at 20 years in 10% of recipients. Even without insulin independence, individuals with sustained graft function reached HbA_{1c} targets with 75% lower insulin requirements and protection from severe hypoglycaemia. Risks were mainly related to immunosuppression: stage 5 chronic kidney disease (7%), severe infections (13%), and skin cancers (10%). These individuals also experienced improved quality of life and reduced diabetes distress and fear of hypoglycaemia; reduced fear of hypoglycaemia being mediated by decreased glycaemic variability.[6,7] While there have been no direct comparisons, islet transplant recipients have more time-in-range and less glycaemic variability than individuals using automated insulin delivery systems.[8] The potential benefits and limitations of both approaches are contrasted in the table.

Current challenges with islet cell transplantation include a limited supply of donor pancreata, long-term decline of graft function, and the requirement for immunosuppression. Clinical trials show that stem-cell-derived islet clusters can attain insulin independence, addressing the donor supply issue.[9] Substantial efforts designed to reduce or avoid the need for chronic immunosuppression are being tested in phase 1/2 clinical trials. These include encapsulation with advanced biomaterials and nanotechnology, and gene-editing (table). Other approaches, such

	Automated insulin delivery systems	Cell therapy
Advantages	Reversible; improved glycaemia compared with multiple-daily injections with continuous glucose monitoring and sensor-augmented pump therapy; no procedural requirements; no immunosuppression requirement	Physiological insulin secretion; potential for insulin independence; reduced severe hypoglycaemia potential; reduced glycaemic variability and improved glycaemia (even when insulin required); improvement or stabilisation of microvascular complications
Disadvantages	Constant device attachment, with alarm and device burden; training requirements; ongoing system maintenance and technical burden; ongoing disease burden with potential requirement for ongoing close follow-up; delayed insulin absorption and longer duration of insulin action of subcutaneous insulin; potential inaccuracies with continuous glucose monitoring; residual glycaemic variability; residual hypoglycaemia and diabetic ketoacidosis risk; potential for skin reactions to adhesives (contact and allergic dermatitis) and issues with insulin absorption or cannula reactions	Shortage of donor organ supply and long wait times; limited eligibility criteria; ongoing long-term follow-up and monitoring, long-term immunosuppression and associated risks (infections, cancer, or chronic kidney disease); procedural risks (bleeding or thrombosis), which might require repetition; potential for graft failure and requirement for insulin therapy or automated insulin delivery system
Future considerations	Improvement in device interface and simplicity of technology; improvement in alarms and safety features of devices; reduced bolus and announcement burden with fully closed loop systems; further developments and clinical testing of bi-hormonal (insulin or glucagon) artificial pancreas systems; integration with artificial intelligence; miniaturisation of technology and potential for implantable devices with intra-peritoneal insulin delivery	Stem-cell derived islet clusters; immune islet or islet cluster encapsulation with devices, biomaterials, and nanotechnology; gene-editing techniques; immunotherapies; new sites for transplantation; expanded use in kidney transplant recipients; nanotechnology to allow real-time tracking of engraftment and immune response
Key future requirements	Preservation or replacement of endogenous insulin production; reduction in disability of insulin deficiency with improved quality of life and reduced disease burden with ability to offer spontaneity and flexibility in lived experiences; consideration for long-term sustainability and equitable access	Preservation or replacement of endogenous insulin production; reduction in disability of insulin deficiency with improved quality of life and reduced disease burden with ability to offer spontaneity and flexibility in lived experiences; consideration for long-term sustainability and equitable access

Table: **Advantages, disadvantages, and future considerations and requirements for automated insulin delivery systems and cell therapy for the treatment of type 1 diabetes**

as newer immunotherapies and local delivery of immunosuppression, are being tested in preclinical models. However, progress will be slow if clinical trials necessary for regulatory approval continue to be restricted to individuals with current indications for clinical islet cell transplantation.

As disease-modifying treatments to prevent type 1 diabetes emerge, we envisage a future where treatment focuses on reversing the disability of insulin deficiency and improving quality of life, not merely glycaemic targets. Thus, future trials on biological treatments and advanced therapeutic medicinal products should assess person-reported outcome measures and lived experiences, in addition to clinical outcome markers. These measures need to holistically capture the effects on quality of life and disease burden. There is an urgent need for validated instruments to assess person-reported outcome measures in people who receive cell therapy and might no longer take insulin. A consensus is required to establish what successful therapy looks like for people with type 1 diabetes, particularly concerning the benefit–risk balance of treatments involving immunosuppression. It is essential to establish endpoints that inform regulators and funders about the safety and effectiveness of new therapies that preserve or replace β cells. Such standardised person-reported outcome measures and quality of life measures should also be incorporated into health economic evaluations for cell therapy.

In addition, identifying further ways to improve patient experience of cell therapy will be important. These include considerations, such as alternative transplantation sites that might offer more convenient delivery, retrieval, and monitoring with similar benefits compared with cell therapy delivered via the hepatic portal vein. Simplifying monitoring of graft function—eg, with single-point laboratory assessments via validated composite scoring systems or novel biomarkers—could improve patient experience.[10] Equitable access to advanced diabetes treatments will undoubtedly be a challenge within countries and more so when considered globally.

Can cell therapy be justified for all people with type 1 diabetes ? Can it deliver benefits beyond a reduction in HbA_{1c} and hypoglycaemia risk? Who gets to decide? A person-centred approach with consideration of reduced burden and enhanced quality of life will be essential to address these questions. Just as automated insulin delivery systems were accelerated by the diabetes community united under #WeAreNotWaiting, and according to the mantra #NothingAboutUsWithoutUs, the voice of people with diabetes will be key in defining

effective endpoints for future trials and clinical criteria for consideration of cell therapy. Let us ensure that clinicians do not impede progress.

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