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Economics of Beta-cell Replacement Therapy

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Abstract:

Purpose of Review: Type 1 diabetes impacts 1.3 million people in the United States with a total direct lifetime medical cost of $133.7 billion. Management requires a mix of daily exogenous insulin administration and frequent glucose monitoring. Decision making by the individual can be burdensome.

Recent Findings: Beta-cell replacement, which involves devices protecting cells from autoimmunity and allo-rejection, aims at restoring physiological glucose regulation and improve clinical outcomes in patients. Given the significant burden of T1D in the healthcare systems, cost-effectiveness analyses can drive innovation and policymaking in the area.

Summary: This review presents the health economics analyses performed for donor-derived islet transplantation and the possible outcomes of stem cell-derived beta cells. Long-term cost-effectiveness of islet transplantation depends on the engraftment of these transplants, and the expenses and thresholds assumed by healthcare systems in different countries. Early health technology assessment analyses for stem cell-derived beta-cell replacement suggest manufacturing optimization is necessary to reduce upfront costs.

Keywords: Cost-effectiveness, type 1 diabetes, stem cells, early health technology assessment, islet transplant

Introduction

Type 1 diabetes mellitus (T1D) is an autoimmune disease in which the majority of beta cells are destroyed. As a result, secretion of insulin by the pancreas and the control of glucose levels in the blood are impaired [1]. Disease onset occurs most frequently between 6 and 12 years old but can occur at any age [2,3]. With an estimated population of 1.3 million patients, the economic burden of T1D in the United States is considerable. Total lifetime medical costs of T1D management are $133.7 billion, with a total income loss of $289.2 billion [4,5]. These

patients are insulin dependent and are at increased risk of complications, such as amputation, blindness, and kidney failure [6]. Most patients are managed on insulin intensive therapy (IIT) for as long as the clinical complications are not prohibitive.

Therapeutic interventions restoring insulin independence could mitigate related complications and reduce healthcare expenditure. Whole pancreas transplantation, while having demonstrated high rates of rendering patients insulin independent, can have significant complications. Two additional types of interventions have been proposed to restore glucose control with insulin independence. The bioartificial pancreas is a device with continuous glucose sensors that provide information for an automatic calculation of the optimal time of delivery and dose of insulin, and the device delivers insulin autonomously through a pump. However, due to limitations estimating meal content and physical activity, this system still requires some level of user input [7,8]. Beta-cell replacement therapy is an alternative approach to the bioartificial pancreas. The implantation of islet cells would provide both independent sensing and physiologic release of insulin. Three key requirements need to be addressed for optimal cell therapy for diabetes: the provision of unlimited cell sources, protecting the cells from auto- and alloimmunity, and the determination of the ideal implantation site and methodology [8–10].

While there is clear potential for beta-cell replacement therapies to provide clinical benefits, improve patient convenience, and reduce complications associated with IIT, the high upfront costs of transplantation and the need for regular revision of the transplant increase costs. Health technology assessment methodologies, such as cost-effectiveness analysis, are routinely used to evaluate the healthcare benefits of medical technologies and relate them with possible additional costs to the healthcare payers. These models are useful to provide policy guidelines on which interventions should be reimbursed and to which groups of patients [11]. Early health technology assessment (eHTA) studies of beta-cell replacement therapies demonstrate that transplantation would only be cost-effective after 8-10 years of transplant efficacy [6,12]. This long-term cost-effectiveness raises concerns on if healthcare payers will reimburse such therapies [13–15]. The aim of this review is to present the economic investment and incentives behind beta-cell transplantation, either using cadaveric islets or stem cells, combined with the health technology assessment studies in the field. The evidence presented in this review aim at providing cues for innovation in clinical development and reimbursement of cell therapies for T1D.

Beta-cell replacement with cadaveric islets

Islet transplantation attempts from xenogeneic sources date back to the late 19th century. The first attempt at transplantation of sheep pancreas fragments made only minor glycemic impact on the patient, who died days later [16]. The first allogeneic human whole pancreas transplantation would only be performed in 1966 and, since then, over 30,000 pancreas transplants have been performed worldwide [17]. The first autologous human islet transplantation was achieved in 1980, while the first allogeneic islet transplant was performed in 1990. In early transplants, patients had very limited long-term engraftment, with over 90% of patients losing insulin independence less than one year after the transplant [17]. The Edmonton protocol, reported in 2000, was a breakthrough for increased graft survival, due to the utilization of a new class of immunosuppressants, and significantly higher doses of islets. While most patients did not retain insulin independence for more than 5 years, the high levels of C-peptide secretion were protective against severe hypoglycemia [17]. As of 2013, 1,584 islet transplants had been performed worldwide. Islet transplantation is a standard clinical procedure in Canada, Australia, United Kingdom, Switzerland, France, Italy, and other European countries [13,18,19]. In the United States, it is still considered an experimental procedure. However, recent Phase III clinical trials demonstrated that islet transplantation is safe and efficacious for glycemic control in patients with severe hypoglycemia, which may change how the United States considers the procedure [13,20].

A major limitation of islets collected from donors is the shortage of available pancreases and variable organ and cell quality [9,10]. The pancreas is the organ with the lowest donation rate per 100 eligible deaths, with approximately 12 donors per 100 eligible deaths being recorded in 2016. With 10,717 eligible deaths that year, this means that only 1,283 new pancreases were made available for transplantation [21]. Following the Edmonton protocol, over 5,000 islet equivalents (IEQ) need to be infused per kg of patient body weight for each transplantation [22,23]. As each pancreas yields, on average, 368,693 IEQ, one or more pancreases need to be processed to provide the dose necessary for a single patient islet transplantation [24]. This translates to only a very small subset of the T1D population in the US being able to benefit from islet transplants.

Several comparative analyses of the costs of islet and pancreas transplantation exist worldwide. In the United States, an analysis that included complications and second islet transplants revealed that the total costs of

islet transplantation are similar to the pancreas transplantation costs for a 4-year timespan after the first transplant (US $138,872 vs $134,748) [25]. The costs of islet cell transplantation in other countries, where the procedure is standard of care, are lower. A value of 347,297 NOK (US $41,675) per islet cell transplant was reported in Norway [26]. In Canada, average costs of 94,765 CAD (US $71,073) were estimated [27]. Results from a clinical trial in France and Switzerland reported costs per transplant of 77,745 EUR (US $87,851) [28]. A comparative cost analysis of whole pancreas transplantation in these countries is not available. The costs of islet cell transplantation are significantly higher than the annual costs of insulin per patient. For example, as of 2017, insulin costs $9,601 in the United States per patient per year [29]. However, the rising costs of insulin, increasing by 200% between 2002 and 2013 [30], call for the assessment of cost-effective alternatives, such as islet transplantation.

Only a few cost-effectiveness analyses have been conducted on human islet cell transplant (Table 1). Cost-effectiveness analyses require a long time span, particularly in the evaluation of expensive procedures, such as transplantations. For this effect, these studies are performed with a discount rate, i.e., increase in direct costs yearly since the beginning of the study, at a rate similar to the yearly inflation rate [31]. We focus on cost-effectiveness analyses of interventions where one, or more, human islet cell transplantations were compared against IIT. The first study was by Beckwith et al [6] and used a US payer perspective. Data from the Diabetes Control and Complications Trial (1990-1993) and from 30 patients who received islet transplantation were used for the determination of probabilities of complications and to estimate the maintenance of graft function. This study provided a positive view on the cost-effectiveness of islet transplantation over IIT, given that the transplant became cost-saving after 9 to 10 years, and cost effective at a willingness-to-pay threshold of $100,000/QALY. However, major criticisms of this study were that it was assumed that patients would require only one transplant over their lifetime, and that graft function would be perfect over its lifetime. These assumptions underestimate the lifetime costs associated with islet transplantation. In contrast, Wallner et al [27] modeled the cost-effectiveness of patients with up to 4 transplants over their lifespan from a Canadian payer perspective. On average, while islet transplantation was more effective than IIT, with an average gain of 3.3 life-years, the cumulative additional costs of transplantation result in an average incremental cost-effectiveness ratio (ICER) of CAD 150,006/QALY (US $112,504/QALY), a value significantly above the considered willingness to pay threshold for cost-effectiveness of CAD 100,000/QALY (US $75,000/QALY). This study recommended additional research on the procedure and medication-related costs as a means to improve the likelihood of cost-effectiveness. Finally, a study was started in

France in 2016 that aims at collecting data on graft effectiveness and evaluating the short-term cost-effectiveness of islet cell transplantation compared to IIT using sensor-augmented pump therapy [32]. While the current literature on the economics of beta-cell replacement using cadaveric islets is scarce, these studies showcase the need for successful long-term engraftment of the cells, preferably with the need for only one transplant, to enable the chance of it being a cost-effective strategy for improved diabetes outcomes. The need for transplant revision, with its high associated costs, renders this approach economically impractical, which should be especially a concern for countries with a limited budget and low willingness to pay thresholds.

Stem cell-derived beta-cell replacement

An alternative to human-derived beta-cell replacement is stem cell-derived beta-cell replacement, which could provide an unlimited pool of islet cells, or pancreatic progenitors of these cells, from directed differentiation of pluripotent stem cells [9]. Both embryonic stem cells and induced pluripotent stem cells have been studied as starting materials for differentiation into insulin-secreting cells. These cells can be multiplied (i.e., expanded) for several generations at a high rate with cell culture flasks [33]. Scientific breakthroughs over the last decade allowed the establishment of protocols with high differentiation efficiency into pancreatic progenitors [33,34] or islet cells [35–37]. Past studies report that a single vial of 10 million pluripotent stem cells can be used to develop a high volume of functional islet cells due to use of platforms such as spinner flasks and bioreactors [34–36,38,39]. These advancements led to the creation of companies aiming at creating products based on stem cell-derived pancreatic progenitors or islet cells from pluripotent stem cells, such as ViaCyte, Inc [40], Semma Therapeutics [41], and Seraxis [42]. From these companies, only ViaCyte, Inc has advanced to Phase I/II clinical trials as of 2019. Data was released in 2018 from ViaCyte, Inc for its Phase I/II clinical trial with PEC-Encap™, a macroencapsulation device protecting cells from autoimmune destruction and allo-rejection, containing pluripotent stem cell-derived pancreatic progenitors. While the devices were deemed safe and two patients still had some cell survival 2 years after the device implantation, the efficacy of its product was dampened because of limited engraftment, due to cell death in the devices and lack of evidence of insulin production. The device design induced a fibrotic foreign-body response, leading to poor transport of various molecules (such as oxygen) across the device membrane, essentially suffocating the encapsulated cells. The findings of this trial led to new preclinical research toward a more effective

encapsulation system [43]. In the meantime, ViaCyte has also launched a second trial, using an open device to allow host vasculature to enter and integrate with the implanted cells while placing the patients under immunosuppression [44].

Given that there are not large-scale efficacy trials available yet for stem cell-derived beta-cell replacement, health technology assessments of this technology have relied on assumptions that its efficacy will be similar to cadaveric islet cell approaches (Table 2). These works fall in the scope of the emerging area of early health technology assessment (eHTA). This approach aims to determine the value of the technology under development in three ways: (i) aid in decision-making on the further development of this technology, (ii) define the acceptable performance indications in comparison to currently available technologies and (iii) provide cues about prospective pricing and reimbursement [7].

The first work in this field was performed by Archibald and Williams from a UK payer perspective [12]. The new technology introduced was induced pluripotent stem cell-derived beta cells, with or without immunosuppression requirement, in comparison with IIT. It was initially assumed that the cost of manufacturing induced pluripotent stem cell-derived beta cells was equal to manufacturing human islets (US $99,629, or GBP 61,770), with the same clinical effectiveness as reported by Beckwith et al [6]. When the requirement for immunosuppression was present, the cumulative costs of the stem cell-derived therapy would fall below the costs of IIT after 9 years of transplantation. After the 20 year follow-up period, it was estimated that stem cell-derived therapy would cost GBP 59,087/QALY (US $76,813/QALY), which is less than IIT. When immunosuppression requirements are removed, cost-savings with stem cell-derived therapy were reached after 8 years. In order to account for variability in the final price of stem cell-derived therapy and a profit margin from manufacturing costs, increasing its initial price $200,000 would make stem cell-derived therapy cost-saving after 11 years of administration.

A second study by Wallner et al [45] increased the complexity of cost-effectiveness analyses of stem cell-derived therapy by combining strategies for manufacturing these cells, under the scope of bioprocess modeling, and the impact of production scale. In general, the increase of production scale led to decreases in manufacturing costs per dose in cell therapies, similar to the effects of production scale in other industries [46]. The authors simulated a manufacturing protocol for embryonic stem cell-derived pancreatic progenitors encapsulated in a pouch made of a

biocompatible material, like the PEC-Encap™ product from ViaCyte. This scheme eliminated the costs of immunosuppression required in a study from the same group analyzing human islets [27]. When considering manufacturing costs of large-scale manufacturing of pancreatic progenitors, the long-term cost-effectiveness analysis at a 0% discount rate (i.e., not adjusted for inflation or the discounted value of future costs) enabled cost-effectiveness of products manufactured in such way, with a WTP of CAD 100,000/QALY. This study highlighted the relevance of manufacturing scale and supply chain considerations for eventual cost-effectiveness stem cell-derived therapy to be reached.

A 2019 published study has included a more comprehensive view of process and accessibility bottlenecks to stem cell-based therapies in type 1 diabetes by using a custom-made open source tool for eHTA of stem cell therapies (TESSEE – Tool for Early Stem Cell Economic Evaluation, http://github.com/catiabandeiras/TESSEE) to [47]. In this study, three combinations of annual demand and number of patients treated by production batch were simulated for a pluripotent stem cell-derived device containing beta cells. At a minimum manufacturing cost of devices per patient of $160,000, cost-effectiveness of these devices was simulated, considering that the reimbursement price would be five times the manufacturing costs and that the clinical effectiveness would be the same as cadaveric islet cells. The therapy was deemed cost-saving over a 20-year period for 2% of the simulated patient population, related to the prevention of end-stage renal disease, because the costs of manufacturing were high. Only 3.4% of the population was deemed cost-effective for the application of the stem cell-based therapy at a willingness to pay threshold of US $150,000/QALY. The reduction of the manufacturing and reimbursement price was shown to be the critical factor for cost-effectiveness, as a reduction of these costs by 75% of the initial value would enable the therapy to be cost effective for over 50% of the study population.

These studies showcase that, even if stem cell-based therapies for type 1 diabetes perform as well in the clinical setting as their cadaveric islet counterparts, the costs of producing these therapies need to be significantly reduced to enable widespread access to these therapies. Additionally, the limited engraftment of these therapies shown in the initial clinical trial requires a simultaneous optimization of large-scale manufacturing of cells and devices while improving the clinical effectiveness.

Conclusions:

Beta-cell replacement therapies, involving devices protecting cells from autoimmunity, are promising for long-term glucose control without the need for exogenous insulin administration. The administration of islets from human donors is approved in several countries and provides added clinical benefits. However, the shortage of donors available has driven the necessary evolution of this therapy toward stem cell-derived beta-cell administration.

From the few studies reporting cost-effectiveness analyses of beta-cell replacement therapy, it is noticeable that the high upfront costs of transplantation only render this therapy cost-effective, or cost-saving, in comparison with IIT after several years. Also, its cost-effectiveness is highly dependent on the healthcare system, the number of transplants required, the elimination of the immunosuppression requirement through effective encapsulation, and the efficacy of glucose control. Budget impact studies and stratification of the therapy for groups of patients with a higher risk of severe complications from hypoglycemia unawareness would provide added value. Additionally, the fact that cost-effectiveness is only noticeable after several years raises concerns on how these therapies are reimbursed, enabling discussions over risk shared agreements and value-based pricing in the United States, if the FDA approves islet transplantation in the United States.

Stem cell-derived beta-cell replacement would eliminate problems with supply and technology advances may eventually drive down manufacturing costs, thus allowing more patients to benefit. Early health technology assessments are being performed under the assumption that these transplants would have the same efficacy as the human islet transplants, which may be overly optimistic. Two reasons that might limit the efficacy of stem cell derived beta cells are the possibility of teratoma growth through undifferentiated pluripotent stem cells in the product, and the generation of heterogeneous undesirable cell populations with reduced insulin secretion efficiency and other potentially unwanted secreted compounds [48]. Additionally, the ethical concerns of the utilization of embryonic stem cells as primary materials for beta-cell manufacturing should be considered [49]. These limitations could be overcome by induced pluripotent stem cells, at the expense of a high cost due to the need for reprogramming somatic cells into pluripotent stem cells. However, it is expected these costs will be decreased over time from increased reprogramming efficiencies and the establishment of high-throughput automated systems [50]. Challenges with scalable manufacturing, purification of differentiated cells to eliminate undesirable cell populations,

device design with proper engraftment and immune shielding, and determination of an appropriate supply chain need to be addressed before scalable stem cell-based devices are a reality. Early health technology assessment works combining bioprocess modeling and cost-effectiveness analysis are invaluable to suggest cues for technological innovation and policymaking in the field.

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Compliance with Ethical Standards

Conflict of Interest
Albert J. Hwa, Joaquim M.S. Cabral, Frederico Castelo Ferreira, and Stan N. Finkelstein declare that they have no conflict of interest.
Catia Bandeiras reports personal fees from Compass Biomedical (fees paid for registration and poster presentation for two conferences in the field of stem cell bioprocessing [Biotech Week Boston 2017 and ISCT 2018]; the presented works are not related to the field of diabetes, as showcased in this manuscript.
Robert A. Gabbay reports being a consultant for Sanofi, and on the Advisory boards for Health Reveal, Onduo, Hygeia, and Lark.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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** Of major importance

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Table 1. Description of the cost-effectiveness studies for beta-cell transplantation from cadaveric islets in comparison with insulin intensive therapy (IIT)

Source / country	Study population	# of islet transplantations /patient	Time horizon/discount rate	Willingness to pay threshold	Incremental cost-effectiveness ratios (ICER)
Beckwith et al, 2012 (USA) [6]	20-year old adults with hypoglycemia unawareness	1	20 years; 3%	US $100,000/QALY	Cost-saving after 9-10 years of transplant; Cost-effective after 2 years
Wallner et al, 2016 (Canada) [27]	Average age 47, adults with hypoglycema unawareness	Up to 4	62.5 years; 5%	CAD 100,000/QALY (US $75,000/QALY)	CAD 150,006/QALY (US $112,504/QALY)
Lablanche et al, 2017 (France) [32]	Adults with severe hypoglycemia	1	1 year; N/A	EUR 20,000/QALY (US $22,600/QALY)	Pending clinical trial completion in 2020

CAD – Canadian Dollars; EUR – Euros.

Table 2. Description of the early health technology assessments for beta-cell transplantation derived from pluripotent stem cells in comparison with insulin intensive therapy (IIT)

Source / country	Study population	# of islet transplantations /patient	Time horizon/discount rate	Willingness to pay threshold	Incremental cost-effectiveness ratios (ICER)
Archibald & Williams, 2015 (United Kingdom) [12]	20-year old adults with hypoglycemia unawareness	1	20 years; 3%	GBP 20,000/QALY (US $26,200/QALY)	Cost-effective after 8 years when cost of goods of stem-cell derived therapy are similar to human islets + no immunosuppression
Wallner et al, 2018 (Canada) [45]	Average age 47, adults with hypoglycema unawareness	Up to 4	62.5 years; 0, 3 and 5%	CAD 100,000/QALY (US $75,000/QALY)	Cost-effective for large-scale manufacturing + 0% discount rate
Bandeiras et al, 2019 (USA) [47]	18-35 years old, hypoglycemia unawareness	Up to 3	20 years; 3%	US $ 50,000 – 150,000/QALY	Cost-saving for 2% of population (high risk of end-stage renal disease). Cost-effective for 3.4% of population at $150,000/QALY.

CAD – Canadian Dollars; GBP – British pounds.