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Review Article

An Update on Type 1 Diabetes Treatments: Insulin Treatment, Cell Therapy and Transplantation

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ABSTRACT

Diabetes is one of the major life-threatening health problems worldwide today. It is one of the most fast-growing diseases that cause many health complications and a leading cause of decreasing life expectancy and high mortality rate. Many studies have suggested several different types of intervention to treat Type 1 diabetes such as insulin therapy, islet transplantation, islet xenotransplantation and stem cell therapy. However, issues regarding the efficacy, cost and safety of these treatments are not always well addressed. For decades, diabetes treatments with few side effects and long-lasting insulin independence has remained one of the most challenging tasks facing scientists. Among the treatments mentioned above, application of human islet transplantation in patients with type 1 diabetes has progressed rapidly with significant achievement. Again, the lack of appropriate donors for islet transplantation and its high cost have led researchers to look for other alternatives. In this review, we discuss very pertinent issues that are related to diabetes treatments, their availability, advantages, disadvantages and also cost.

Keywords: Cell therapy, diabetes economy, diabetes treatments, insulin, islet transplantation, stem cell therapy

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INTRODUCTION

Diabetes mellitus is a life-threatening disease that might be complicated by cardiovascular and kidney diseases, ketoacidosis and skin conditions (Habener, 2004; Nathan et al.,

2009). Diabetes mellitus is a fast-growing metabolic disease (Kaul et al., 2013; IDF, 2015). In 2015, the International Diabetes Federation estimated that worldwide, more than 415 million people live with diabetes and 5% of that population are diagnosed with type 1 diabetes (IDF, 2015; ADA, 2017). The incidence of diabetes is dramatically increasing and predicted to more than double by the year 2040 (IDF, 2015). Patients with diabetes are costly to maintain and in 2015, it was shown to be an economic burden on the health maintenance schemes of undeveloped and developed countries, amounting to USD673 billion per annum, which is equivalent to 12% of total health expenditure (Guariguata, 2012). In Malaysia, prevalence of diabetes is growing and is expected to rise to 21.6% of the adult population by 2020. Statistics show that patients with type 1 diabetics are 0.6% of the whole population with diabetes in Malaysia (IDF 2015).

Diabetes is a chronic disease caused when the pancreas either does not produce sufficient insulin or the body fails to use insulin (IDF, 2017). Insulin facilitates cellular uptake of glucose and regulates carbohydrates and fat metabolism. In type 1 diabetes, insulin secreting cells are destroyed by autoimmune attack (Table 1). Although insulin injections or treatment using synthetic medication may temporarily control diabetes, these drugs cannot cure the disease.

Table 1
Autoantibodies against pancreatic antigens in type 1 diabetes

Auto-Ab	Abbreviation	Antigen Expression	Explanation
Anti-insulin Abs	IAA	Pancreas	Detected in 50% type 1 diabetic children
Anti-glutamate decarboxilase Abs	GADA	Pancreas and nervous system	Found in 70%-80% newly diagnosed diabetics
Anti-insulinoma associated 2 Abs	IA2-A	Pancreas	Found in about 60% of type 1 diabetics
Anti-islet cell Abs	ICA	Pancreas	Detected in about 70%-80% newly diagnosed type 1 diabeticd
Abs against the zinc channel ZnT8	SCL338A	Pancreas	-

(Akerblom et al., 2002; American Association for Clinical Chemistry, 2016).

Recently, cell therapy was deemed to hold great potential for developing a permanent cure for diabetes. One of the most recent successes in cell therapy is islet transplantation in the bile duct of the liver in type 1 diabetics (Malka et al., 2000; Margener & Baillie, 1997). However, the main problem with this treatment method is the lack of compatible human islet sources for transplantation. Stem cells such as embryo and adult stem cells that can potentially differentiate into insulin secreting islet-like clusters and xenogeneic islet have shown some promising results for treatment of diabetes (Habener, 2004). However, the success of cell therapy in treating diabetes is limited by the lack of human pancreatic β-cells to produce insulin. Alternatively, it was suggested that other animal species could be used as sources of pancreatic β-cells. It was demonstrated in diabetic mice that some β-cells, for example, embryo blastocysts and

pancreas, liver, bone marrow and islet cells, from various mammalian species have the potential to reverse symptoms of diabetes (Wedemeyer et al., 2016).

Insulin and Cell Therapies for Diabetes

In the early 1920s, the extract of bovine pancreas cells injected in a diabetic patient reduced diabetic signs such as glycosuria and hyperglycemia. In 1921, insulin was discovered by Frederick G. Banting (Karamitsos, 2011). Since the advent of genetic engineering, many useful immunoproteins and hormones, including biosynthetic human insulin (Sara et al., 1998), can be prepared by recombinant DNA techniques and produced in various efficient expression systems including bacteria, yeast and mammalian cells (Razis et al., 2006; Abdul Razis et al., 2008, Tam et al., 2012). Direct treatment with naked DNA containing the gene of interest, the insulin gene, into the host tissue or selected organs is possible but this method faces a lot of uncertainty in terms of potential integration in the host genome that may lead to unwanted cell transformation. Until now, biosynthetic insulin and its analogues serve as the mainstay in diabetic treatment. Insulin therapy reduces diabetic signs; however, diabetics require frequent monitoring of blood glucose while experiencing various side effects, including hypoglycemia (Cryer et al., 2009), unusual ocular disturbance (Lee & Traboulsi, 2008), lipohyperthrophy (Blanco et al., 2013), hypersensitivity (Wong et al., 2007), anaphylaxis (Ghazavi & Johnston, 2011), hypertension (Arima et al., 2002), weight gain (Russell-Johnes & Khan, 2007), myocardial infarction (Malmberg et al., 2005), renal dysfunction (Patrick et al., 1992), hemolytic anemia (Dhaliwal et al., 2004) and gastrointestinal distress (Drugs, 2017).

Edmonton Protocol

In 1972, Lacy et al. (1972) showed that transplantation of islet allografts in the portal vein of pancreactomised patients reduced insulin independence for long periods. In 2000, the Edmonton Protocol was introduced by a University of Alberta research group (Shapiro et al., 2000; McCall & Shapiro, 2012). The Edmonton Protocol is a method of implantation of pancreatic islets for treatment of type 1 diabetes mellitus. This protocol reduced the risk of islet graft rejection and inhibitors such as inadequate islet cluster, insufficient prophylaxis, diabetogenic consumption and drugs that prevented attainment of insulin independence (Shapiro et al., 2000). According to the protocol, in order to gain sufficient islet quantity and complete insulin independence, islets of two to four donors are required to be harvested and transplanted into recipients. The optimum islet number for transplantation in type 1 diabetics is approximately 11,000 IEQ/kg body weight. In this protocol, the period of cold ischemia and the need for exposure to xenoprotein such as fetal calf serum, were minimised and the islets could be transplanted immediately after harvest without need of prior long-term freezing or *in-vitro* maintenance (Gaglia, Shapiro, & Weir, 2005). The Edmonton Protocol success rate is 80% with insulin independence during the first year, although in the long term the results are quite varied (Ryan et al., 2002; Shapiro et al., 2006).

Stem Cell Therapy

Stem cells are unspecialised cells of multicellular organs with potential for differentiation into other cell types during the embryonic period or in adults. Pluripotent and multipotent stem cells can differentiate to other types of cell tissue to repair dysfunctional cells or maintain tissue or organ sustainability (Habener, 2004; Fuchs et al., 2004; Wagers & Weissman, 2004; Young et al., 2004). Stem cells have three main properties, which are, multipotency as in adult tissues, pluripotency as in the blastocyst of embryos and totipotency as in a fertilised egg. The most distinguishable characteristic of stem cells is their capacity for self-renewal, transmutability to other cell types, extreme motility and immune resistance in the host (Habener, 2004; Abraham et al., 2004; Yang, 2004).

Islet progenitor cells (IPC) are found not only in the islets but also in the ducts and acinar tissue of the pancreas (Tang et al., 2004; Pessina et al., 2004). The bone marrow, liver, umbilical cord blood cells and embryo stem cells are the origin of IPC. The IPC differentiate into an islet-like cluster (ILC) and is shown *in vitro* to have huge potential of proliferation and insulin secretion upon exposure to growth factors such as fetal serum, epidermal growth factor (EGF), nerve growth factor (NGF) and fibroblast growth factor (FGF). Treatment with proliferation and differentiation inhibitors provides the ILC with the ability to express and secrete insulin, glucagon, somatostatin, glucagon-like peptide-1 (GLP-1) and pancreatic polypeptide (PP) (Lechner & Habener, 2003). In addition, primary epithelial cells harvested from the skin, umbilical cord and intestine also have the capacity to differentiate into islets when maintained in the appropriate environment and culture medium. However, the insulin production and functionality of these epithelial cells are lower than that of native pancreatic islets (Lechner & Habener, 2003).

Islet precursor cells in the adult pancreas has been suggested to impact pancreas development during embryonic damage, such as those caused by surgery and drugs (Dor et al., 2004). Pancreatic β-cells can still maintain insulin secretion even in cases of insult to pancreatic tissues (Dor et al., 2004). Multipotent stem cells can regenerate new cells from damaged islets and can most probably differentiate into functional β-cells (Dor et al., 2004).

Islet Transplantation

Islet transplantation has been suggested to be the ultimate treatment for the recovery of glucose homeostasis in patients with type 1 or late type 2 diabetes (Figure 1). Functional transplanted islets alleviate hypoglycemia and reestablish glucose homeostasis through the restoration of insulin production. Type 1diabetes can be cured by pancreas replacement. This was shown in pancreactomised diabetic dogs transplanted with fragments of the pancreas beneath the skin. The grafts kept the dogs alive even though they were not in physical contact with the digestive organs. This procedure was used in human experimentation with the grafting of sheep pancreas in a patient with type 1 diabetes. Unfortunately, although the graft improved the glycosuria, the patient did not survive after falling into adiabetic coma (Gaglia et al., 2005).

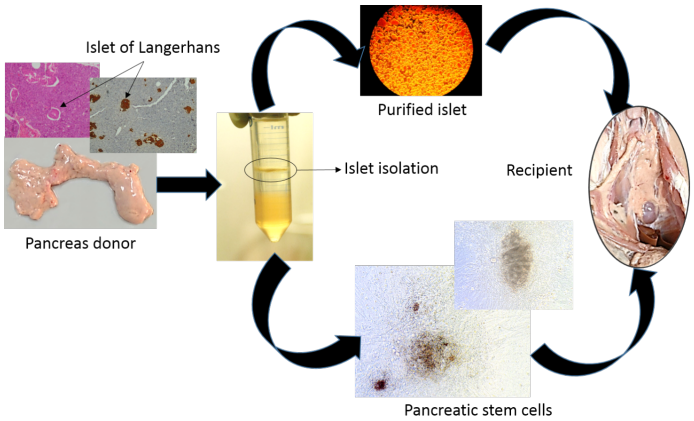

Figure 1. Cell therapy procedure in type 1 diabetes. Pancreata are collected from donors (human or animal), then islets or stem cells are harvested from pancreas. After islet purification and stem cell growth in culture, viable islets or cells are transplanted into the recipients' body

The use of improved surgical procedures and immunosuppression drugs have increased the success rate of vascularised intact pancreas transplantation. Between 1988 and 2016, there were 29,962 cases of successful vascularised pancreas transplantation worldwide (United Network for Organ Sharing, 2016). However, the use of islet transplantation to achieve insulin independence and alleviate complications of type 1 diabetes is suggested to be superior to whole pancreas transplantation or insulin therapy. Islet transplantation causes fewer complications and side effects than insulin therapy and it is easier to perform compared to whole pancreas transplantation. Insulin therapy is effective only if the patient fully subscribes to the consumption protocol and dosage and follow-up regimen and is supervised by a professional healthcare team. It should be noted that the aim of pancreas or islet transplantation is to achieve insulin independence, increase quality of life and diminish secondary diabetes complications (Robertson et al., 2010). At the early stages of islet transplantation experiments using induced diabetic rodents as models, the islets were shown to reverse diabetes. Transplantation of islet allografts at various sites on the body of diabetic rodents temporarily improved insulin requirement, but did not reverse diabetes for a period long enough to achieve complete insulin independence (Ballinger & Lacy, 1972; Najarian et al., 1977).

Islet Xenotransplantation in Diabetes

Currently, islet allotransplantation procedures are limited by lack of donor sources (Collaborative Islet Transplant Registry, 2009; Shapiro, 2011; Thompson et al., 2011; Hani et al., 2010; Hani et al., 2014). For that reason, over the last decade, fewer than 1000 islet transplantation procedures have been performed worldwide (Collaborative Islet Transplant Registry, 2009). To overcome the shortage, alternative sources of islets have been proposed including pigs, non-human primates, cattle, sheep, goats and fish (Hani et al., 2010; Hani et al.,

2014; Vakhshiteh et al., 2013; Hani e al., 2015; Hani et al., 2016; Hani et al., 2017; Kean et al., 2006). Although the best source of islets for human transplantation are non-human primates, due to issues like genetic homogeny, and ethics, safety and logistics, other sources have been investigated. Pig islets are one potential source for xenotransplantation for humans because of compatibility based on similarity to insulin molecules and glucose kinetics between these species (van der Windt et al., 2012). However, among Muslims, tissues from porcine sources are not generally acceptable for human transplantation.

As with all tissue transplantations, outbred diversity, heterologous immunity and MHC expressions are barriers to long-term xenograft survival; thus, islet transplantation needs to address these issues of immune response and rejection, for instance, through immunosuppression and encapsulation (Thompson et al., 2011).

Safety Issues in Islet Therapy for Diabetes Mellitus

Stem cell therapy. Stem cells such as mesenchymal, embryonic and hematopoietic stem cells, have the potential for differentiation into insulin-secreting or islet-like cluster cells. Some pancreatic islet cells or islet progenitor cells can differentiate into new insulin-secreting cells to replace injured and old β-cells that are undergoing apoptosis (Figure 1) (Kirk et al., 2014). In cell therapy for type 1 diabetes, adult stem cells are probably more suitable than embryonic stem cells. Adult pluripotential stem cells are teratogenic and their use give rise to fewer ethical issues. Adult pluripotential stem cells readily differentiate into the tissue cells of their origin and would be of greater application in cell replacement therapy for diabetes. However, diabetes treatment methods using these stem cells are still not fully developed for use without dire adverse consequences (Habener, 2004).

Safety of islet transplantation. Islets are fraught with the tendency to undergo apoptosis, diminished functionality and viability during purification (Lipsett et al., 2006). The isolation and purification of islets from the pancreas are governed by the presence of growth factors, supportive matrix and physical and chemical stresses, such as osmotic, hypoxia and mechanical stresses, that determine the survival of the cells. Thus, optimisation of the islet isolation procedure is imperative for obtaining viable cells for transplantation.

The success of islet transplantation is also determined by the site on the body, glucose and lipid concentrations (Lipsett et al., 2006) and the immunosuppressive drugs used. Graft sites that are naturally well-nourished and with an environment conducive for transplantation will increase the success of the treatment. In a recent study, the islets were first encapsulated with an immunprotector to avoid destruction by the immune system while retaining their ability to communicate with the environment (Lipsett et al., 2006).

Although anti-rejection regimens for both islet and pancreas transplantation recipients are the same, however, complications arising from pancreas transplantation are higher than from islet transplantation (Moassesfar et al., 2016). Whole pancreas transplantation is most common

for patients with pancreatitis and pancreas dysfunction or failure, while islet cell transplantation is usually recommended for those patients with islet mass loss or destruction, mostly in type 1 diabetes. Therefore, in type 1 diabetes, it is not necessary to transplant the whole pancreas even if it is less costly compared to islet transplantation. As the pancreas is a multifunction organ, if the graft is rejected by the immune system of recipients, then the whole organ, rather than just the islet cells, must be replaced.

Islet xenotransplantation. Safety protocols for islet transplantation are also applicable for islet allotransplantation and xenotransplantation. Among issues associated with transplantation is the transmission of infections. To ensure success of transplantation, precautions have to be taken to avoid transmission of infectious agents from the donor and the environment to the recipient (U.S. Food and Drug Administration, 2003; Mueller et al., 2011). One threat of infection concerns the use of porcine islet cells. Porcine endogenous retrovirus infection in islets is often a threat in xenotransplantation. Other infectious agents such as the cytomegalo virus, herpes virus and lymphotropic herpes virus as well as bacteria that are resident in porcine islets can pose a threat to recipients. Thus, to avoid infections, the animals serving as sources of islets must first be screened to ensure they are free from zoonotic organisms. However, it is often difficult to avoid contamination by infectious agents because the porcine retrovirus genome, for instance, is integrated in the animal genome and can go undetected and in this way, be transmitted to recipients during transplantation (van der Windt et al., 2012; Zhu et al., 2014).

Economics

To ensure the safety of recipients, animals like pigs that are the source of islets must be bred in expensive sterile and clean facilities. It is estimated that a facility complete with the equipment for cleaning breeding of 100 animals can cost more than USD10 million with a maintenance cost of between USD1 to 2 million per year. However, these breeding facilities are necessary to ensure supply of islets that are clean and safe for human use (van der Windt et al., 2012).

Based on reports, the cost of insulin therapy over the long term is higher than islet cell transplantation (Berwick, 2016). In 2016, the cost of insulin therapy was estimated at $71,000 per quality-adjusted life year (QALY) (Berwick, 2016), while for islet transplantation it was estimated at $50,000/QALY. The initial cost of islet transplantation is higher than that of insulin therapy, but over the years, due to continuous and long-term application, the total cost of insulin therapy eventually becomes much higher than that of islet transplantation (Beckwith et al., 2012).

Pancreas transplantation is marginally cheaper at a total cost of USD135,000 than islet cell transplantation at USD139,000. These expenses were calculated based on the cost of transplantation procedures and hospitalisation after surgery (Table 2).

Table 2
Comparison between treatments for type 1 diabetes

Therapy	Type	Global practice rate	Cost	Advantages	Disadvantages
Insulin Injection	Recombinant Animal	23.9 million (2000) 60,000 injections throughout life-time[a]	$663,000/20years $71,000 QALYs[b]	Easy access and personally practicable; Temporarily capable of controlling blood glucose level[c]	Hypoglycemia, unusual ocular disturbance, dermatologic reaction (lipohyperthrophy), hypersensitivity, immunologic response (anaphylaxis), hypertension, weight gain, myocardial infarction, renal dysfunction, hemolytic anemia and gastrointestinal distress[c]
Pancreas Transplantation	Intact Partial	2328/year[d]	$ ~134,750[e] (Mean total cost incorporating complications)	One proper donor may be sufficient[e]	Proper donor shortage; Need surgery; High rejection risk[e]
Islet Transplantation	Auto Allo	<100/year[f]	$659,000/20year $61,000 QALYs $ ~139,000 (Mean total cost incorporating second islet transplants (ITA)[b]	No surgery procedures necessary; Less post-transplantation complication compared to pancreas transplantation; Consistent islet yield[c]	Lack of donors; More than one donor may be needed to achieve insulin independency; Need isolation processing; Transplanted β-islet cells may be rejected within several years and must be repeated every couple of years at a cost of $120,000 per transplant[b,e]
Islet Xenotransplantation	Fatal	Not routinely practised	$60,700 QALYs[b]	No isolation procedure necessary; Proliferation and maturation *in vivo*	Not fully functional until >4 months after transplantation; Nonsurvival C-section in sow; Need for many foetuses
	Neonatal			No need for harmful purification process; Proliferation *in vitro* and *in vivo* after transplantation; Resistance against hypoxia; Preferable breeding logistics	Not fully functional until >4 weeks
	Young			More preferable breeding logistics vs. adult >2 years	Fragility of islets; Difficult to obtain consistent yields; Less preferable breeding logistics vs. neonatal[57]
	Adult			Consistent islet yields	Non-preferable breeding logistics; High costg
Stem cells	Polypotent Multipotent	N/A	N/A	Can be harvested from adult tissues (Habener, 2004); Unlimited sources of β-cell[h]	Teratogenic behaviour; Auto-immune attack by recipient body against autograft stem cells[h]

[a)] Al-Tabakha et al. (2008); [b)] Beckwith et al. (2012); [c)] Insulin side effects (2017); [d)] Estimated number of organ transplantations worldwide in 2014 (2014); e) Moassesfar et al. (2016); [f)] Islet Transplantation Technology (2010); [g)] van der Windt et al. (2012); [h)] Habener (2004).

CONCLUSION

Cell therapy, whether with islets or stem cells, is a promising treatment for type 1 diabetes that could provide long-lasting insulin independence. However, these methods of therapy for diabetics are limited by cell quality, donor availability and financial constraints. In the final analysis, the choice of therapeutic means is governed by reliability of the technique to provide a long-lasting cure for diabetes. Currently, cell therapy is only affordable by the affluent and is not within the means of low-income patients. Given more time and with greater advances in technology, cell therapy for diabetics may be affordable for all.

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