

A Comparison Between Islet And Stem Cell Transplantation For Treatment Of Type 1 Diabetes Mellitus: A Systematic Review

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Abstract

Introduction: The incidence of type 1 Diabetes Mellitus (T1DM) has been increasing rapidly worldwide in the past decade. The current standard treatment is exogenous insulin therapy, however, this procedure is highly associated with poor glycemic control that may lead to life-threatening hypoglycemic episodes. Cellular-based therapy for T1DM has been recently developed, making it pertinent to compare the effectiveness between two most anticipated breakthroughs: islet cell and stem cell transplantation, in order to determine which procedure is more effective.

Methods: A comprehensive digital literature search was performed using PubMed and Ovid Medline for primary research studies published between Jan 2000 – Nov 2015. Relevant cohort, case-control, case series, and in vivo studies were included. The abstracts and full text of the retrieved articles were scanned for potential studies that fulfilled the inclusion criterias. The quality assessment of studies were conducted using ARRIVE, NOS, and MINORS.

Results: Nineteen primary research studies met the inclusion criterias and were assessed for the review. Eleven out of 19, were considered as high-quality, while the rest were moderate-quality. The studies generally reported the insulin independence, graft functionality, and glycemic control. The insulin-independent period for islet cell transplantation was proven to be longer compared to stem cell transplantation with better glycemic control. Stem cells were successfully differentiated into glucose-responsive insulin-producing cells, that also released glucagon and somatostatin.

Discussion: The majority of the included studies were using the same outcome measures which allow a more comprehensive comparison to be conducted. Based on the assessment, islet cell transplantation is currently better. This treatment was found to lead to significant improvements in insulin independence and glycemic control observed through insulin-free period, HbA1c, blood glucose, and C-peptide serum measurement. On the other hand, certain challenges – such as donor shortage and poor engraftment - hinders the widespread application of the treatment. Therefore, stem cell transplantation is thought to possibly be replacing islet cell transplantation in the future. Stem cells had successfully been differentiated into β -like cells that were not only producing insulin, but also glucagon and somatostatin, as well as acting in glucose-stimulated manner, imitating the physiologic mechanism of β -cells.

Conclusion: It is conclusive that islet stem cell transplantation was proven to perform relatively better in terms of insulin independence and glycemic control compared to stem cell transplantation for treating T1DM. Both cellular-based treatments provided relatively better glycemic control compared to the current standard treatment, exogenous insulin therapy. All the studies have reported that both treatments lead to substantial improvement between pre-and post-transplantation periods. Stem cell transplantation was also proven to have unlimited potentials to be the future solution for T1DM. Although, there was limited studies on human subjects, but based on the current available studies, the results were quite conclusive.

Keywords: Type 1 diabetes mellitus, Cellular-based treatment, Islet cell transplantation, Stem cell transplantation, Insulin independence, Glucose stability, Glycemic control.

Introduction

Type 1 Diabetes Mellitus

Diabetes has become a worldwide health problem causing a huge

burden on health system and economy. The incidence of type 1 Diabetes Mellitus (T1DM) varies 50-100 fold around the world [1]. According to Maahs, et al. the incidence has been increasing 2-5% worldwide in the past decade, which accounts for 5-10% of the total cases of diabetes [2]. T1DM is caused by the autoimmune damage of β -cells in the pancreatic islets of Langerhans leading to β -cells dysfunction [3]. The incidence of T1DM in children <14

years of age in 50 countries worldwide accounts for 19,164 cases from a population of 75.1 million children [2].

The loss of β -cells in T1DM results in defects of insulin production causing hyperglycemia leading to several complications, including diabetic nephropathy, neuropathy, and retinopathy. β -cells damage is associated with severe chronic complications with irreversible multi-organ damage [4]. These complications can eventually lead to death, which turns out to make the development of treatment for T1DM important.

The current standard therapy for T1DM is exogenous insulin therapy that is considered unsatisfactory. This treatment does not provide sustained physiological release of insulin - leads to hypoglycemia - and β -cells regeneration [3]. Therefore, cellular-based therapy is a preferred strategy since it achieves better glucose control and also regenerates the damaged β -cells [5].

The obstacles following the cellular therapy development are varied, from the shortage of donor organs, high rate of invasiveness, high rate of rejection, low graft survival rate, until low functional status due to both immune and non-immune-related causes [1,2,4,5]. This systematic review is designed to evaluate and compare between two breakthrough treatments being developed - islet cell transplantation and stem cell transplantation - for T1DM patients based on the strength of evidence observed in current studies.

The Current Available Treatment for Type 1 Diabetes Mellitus Exogenous Insulin Supply

Currently, patients with T1DM are dependent on the exogenous insulin therapy that comes in the form of multiple daily injections (MDIs) or continuous subcutaneous insulin infusion (CSII) using external pump [7].

Exogenous insulin cannot imitate endogenous insulin. In healthy individuals, the liver is exposed to insulin concentrations two to four times higher than the insulin level at the peripheral circulation.⁸ Exogenous insulin supply cannot approach the portal systemic circulation that results in impaired glucose suppression. Moreover, rapid increase of insulin level in the circulation may lead to peripheral hyperinsulinemia which predisposes to hypoglycemia.⁸ Based on data from pediatric studies of CSII, there was still incidence of hypoglycemic episodes and no improvement of HbA1c level, which leads us to consider cellular-based therapy as one of treatment approach without exogenous insulin dependency [8].

Cellular-based Therapy for T1DM

Islet Cell Transplantation

Recent clinical trials have exhibited that islet cells transplantation offers a cure for T1DM with independency from exogenous insulin supply [9]. It is estimated that 70% of transplanted T1DM patients have achieved insulin independence within a time span varied from one to five years [10].

Islet cell transplantation is a promising concept for curing T1DM due to its potential high efficacy and minimal invasiveness [10]. Islet cells control blood glucose by automatically releasing insulin at the appropriate time [10]. The procedure does not require general anesthesia or major surgery [9].

During the post-transplant period, a significant fraction of transplanted islets are lost immediately, therefore to ensure the functionality of the islet grafts, the transplantation protocol requires 10^6 islets which requires up to four donor pancreases [9]. This is one of the limitations of islet transplantation as a treatment option.

Edmonton Protocol

Edmonton protocol consists of multiple infusions of isolated islets from brain-dead donors (BDD), steroid-free immunosuppression, and immediate transplantation without *in vitro* culture.^{9,10} According to a clinical trial conducted by University of Alberta (2000), approximately 10% of patients receiving treatment were able to maintain insulin-free period for five years [10]. After a high number of clinical success, the annual numbers of procedures increased to more than 100 transplantations a year with 85% insulin independent status, however, there are undeniably high concerns on the limited donor supply, side effects of immunosuppressive regimen, and poor long term results [9,10]. Further improvements are necessary to increase the efficacy of the treatment.

Stem Cell Transplantation

Stem cell transplantation has been acknowledged as a feasible treatment for T1DM [5]. Stem cells have been shown to differentiate into insulin-producing cells *in vivo* [5]. Stem cell therapy for T1DM is aimed to substitute β -cells thus restore its functions [4]. Stem cells are able to regenerate pancreatic endocrine cells that might restore the destroyed β -cell pool with β -cells derived from pancreatic and extra-pancreatic stem cell sources [4].

Differentiation of pluripotent stem cells into β -cells

Pluripotency is defined as the ability of the cells to differentiate into different types of specific cells [5]. Stem cells have pluripotent properties, which allow them to differentiate into 200 or so types of cells in the body [5]. Pluripotent cells can be obtained from pre-implantation of embryos – embryonic stem cells (ESCs) - or adults cells undergoing cellular reprogramming - induced pluripotent stem cells (iPS), which is made of fibroblasts that were transfected to four pluripotent-related genes (sox2, klf4, c-Myc, and Oct4), and turned into pluripotent stem cells [5,14].

A small number of pluripotent cell lines have been used to form islets for transplantation, in which these cells would be generated, maintained, and differentiated under GMP-grade condition and expected to expand up to 1 million islets for a single transplantation [12].

Currently, it is still not possible to turn stem cells further into 100% functional β -cells, however, in a study involving streptozotocin (STZ)-induced diabetic mice, the cells that were implanted under

kidney capsule or epididymal fat pad, were capable of secreting C-peptide as a response to glucose after 12 weeks. It is important to note that C-peptide at the normal range indicates good response to tolerance test, which means that even a small amount of insulin production is beneficial for glycemic control [12].

The Objectives

It appears that the previous studies have only addressed in details about the glycemic stability and insulin independence in each study separately, thus it becomes inconclusive whether islet cell transplantation is better than stem cell transplantation for treating T1DM or vice versa. With this in mind, the primary aim of this systematic review was to critically review the prospects of islet cells and stem cells transplantation to become the standard therapy for T1DM, and to compare the efficiency between the two treatment options in controlling glycemia. The qualification criterias to measure the efficiency of the treatments are based on the insulin-independent period, HbA1c levels, C-peptide levels, and blood glucose levels post-treatment.

Methods

Search strategy

A comprehensive computer-based literature search was performed using PubMed and Ovid Medline for articles published from January 2000 to November 2015. The keywords were formed using the Boolean search terms:

- (insulin independence OR insulin free period) AND (graft survival OR autoantibody) AND (normal glucose level) AND (type 1 diabetes mellitus OR type 1 DM OR T1DM)
- (islet cell transplantation) AND (type 1 diabetes mellitus)
- (stem cell transplantation OR stem cell implantation) AND (type 1 diabetes mellitus OR type 1 DM OR T1DM)
- (comparison OR contrast OR testing) AND (islet cell transplantation) AND (stem cell transplantation OR stem cell implantation) AND (type 1 diabetes mellitus OR type 1 DM OR T1DM)

A gray literature of the bibliographies from relevant articles were screened to identify any articles that might have been missed by electronic searches. The glossary can be found in Appendix A.

Study selection

Inclusion criteria

- a)** Cohort, case series, case-control and *in vivo* research articles,
- b)** written in English, **c)** latest publications, **d)** modifications or updates of previously published experiments were considered as new references and included, and **e)** application of previously reported researches comparing procedures.

Exclusion criteria

The studies excluded from this systematic review:

- a.** Systematic reviews and meta-analyses, commentaries, editorials, conference abstracts; and
- b.** Studies with different outcome measures.

Article selection

The studies were screened in two stage, at first the abstract and title

were reviewed, only articles that fulfilled the inclusion criterias were selected to be reviewed in full text. Any articles that did not meet the criterias were immediately removed.

Data extraction

The data extracted from selected articles were the sample size, study design, outcome measures, and the results of treatments. The outcome measures and comparison parameters between procedures extracted for this review includes insulin-free period, C-peptide, HbA1c, and blood glucose levels. Data extraction is conducted using a custom made form specifically designed for this review.

Quality assessment

The methodological quality of the studies were assessed using several different assessment tools:

a. ARRIVE for *in vivo* experimental studies

The use of ARRIVE guideline is intended to improve reporting of *in vivo* studies [15]. ARRIVE consisted of 20 components that have been developed using CONSORT as the foundation. 15 Criteria 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17 correspond to the internal validity, criteria 5, 18, 19, 20 correspond to external validity, while criteria 13 correspond to statistical analysis of the included studies. The criterias were scored using predefined gradings [15]:

- 0 = inaccurate/not concise/clearly insufficient/not clear/no
 - 1 = accurate/concise/possibly accurate/possibly sufficient /clear/adequate/yes
 - 2 = clearly accurate/clearly sufficient/clearly adequate/yes
- in which each component has the maximum score of 2 and minimum amount of 0 [15].

b. Newcastle-Ottawa Quality Assessment Scale (NOS) cohort studies

NOS for case series studies is based on three domains : selection, comparability, and exposure [16].

- Selection of the studies consists of 4 criterias with the maximum score of one star (*) in each component (4/4), and
- Comparability of the studies consists of one criteria with the maximum score of two stars (*) (2/2),
- Exposure of the studies is measured using three criterias with the maximum score of one star for each component (3/3).

The maximum overall grade is the total maximum score from each component (9/9) [16,17].

c. MINORS for case series studies

Methodological Index for Non-randomized studies (MINORS) is used to assess both comparative and non-comparative case series studies, which consisted of 12 components with the first 8 being specifically for non-comparative studies. The items are scored with predefined grading:

- 0=not reported
- 1=reported but inadequate
- 2=reported and adequate

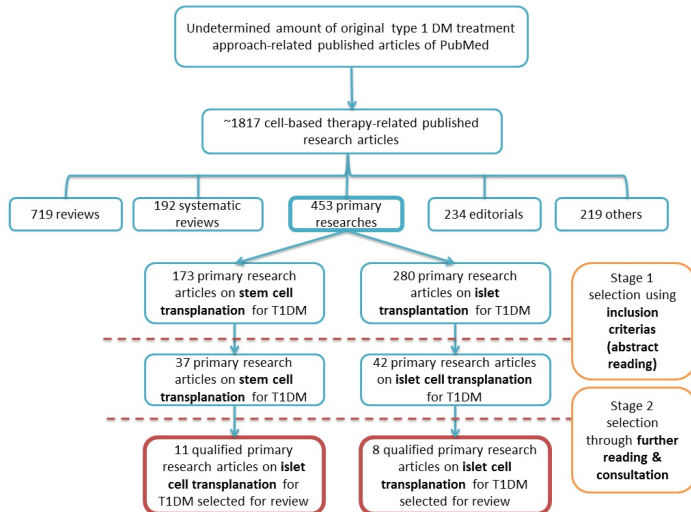
The maximum score is 2 points for each components, with the maximum overall score of 16.

Results

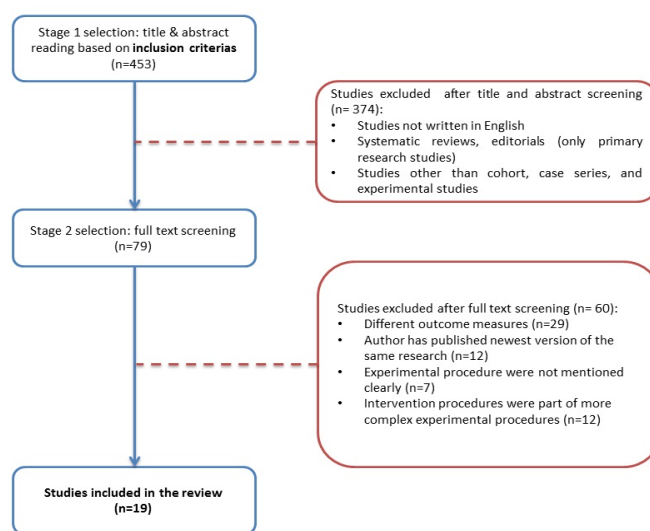
Search findings

The initial literature search from PubMed database yielded 453 potential studies to be included in review. The studies were selected based on the type of study, the language they are written in, and study design. Phase 1 selection shortlisted cohort studies, case series studies, and *in vivo* experimental studies, leaving 37 primary research articles on stem cell transplantation and 42 primary research articles on islet cells transplantation being further reviewed. After a thorough consideration through full text

reading, 29 studies were excluded because the outcome measures being used were different, 12 studies were excluded because the author has published the newest version of the on-going research, 7 studies were excluded because the experimental procedure were not reported clearly, and 12 studies were excluded because the experimental procedures being evaluated were part of more complex experimental interventions. The author ended up selecting 19 qualified articles in total, consists of 11 primary research articles on islet cells transplantation and 9 primary research articles on stem cells transplantation, refer to Flowchart 1 and Flowchart 2 for details.



Flowchart 1: Study selection of primary research articles to be included in review.



Flowchart 2: Study selection from initial search yield of 453 down to 19 primary research articles.

Quality of included studies

The results of methodological quality assessments are presented in Tables 1-5. The studies consisted of 11 cohort studies, one case control study, one case series study, and six *in vivo* experimental studies. All the criteria lists of methodological quality assessments of the included studies are presented in Appendix B.

ARRIVE for *in vivo* experimental study reporting

Based on the quality assessment conducted using ARRIVE, the average rating was 28.8. Rezanian, et al. received the highest rating of 40 for all 20 components, while Soria, et al. received the lowest rating with the total of 25 for all 20 components [26,29]. The ARRIVE criteria least likely to be answered was details on the

Study	Title	Abstract	Introduction	Methods										Results			Discussion			Overall Score (/40)	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19		20
Soria B, et al. 2000 [26].	2	2	1	2	0	1	2	0	0	2	1	2	1	2	2	1	0	2	2	0	25
Sipione S, et al. 2004 [27].	2	2	1	2	0	2	2	0	0	2	1	2	1	2	0	2	2	2	2	0	28
Alipio Z, et al. 2010 [28].	2	2	1	2	0	1	1	2	0	2	2	1	1	2	1	2	0	2	2	0	26
Rezanian A, et al. 2012 [29].	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	40
Kroon, et al. 2008 [30].	2	1	1	2	0	2	2	2	0	2	1	2	0	2	2	2	0	2	2	0	27
Jurewicz, et al. 2010 [31].	2	2	1	2	0	2	2	2	0	2	1	2	0	2	2	2	0	2	2	2	27

Table 1: ARRIVE Quality Assessment for In Vivo Experimental Studies.

Study	Selection				Comparability		Outcome			Overall Score (/9.0)
	Representativeness	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration of outcome was not present at the start of study	Study controls for	Additional factors	Assessment of outcome	Follow-up	Adequacy of follow up	
Shapiro A et al. 2006. [18]	Somewhat representative of the average diabetic patients seeking for transplant in the community ★	no description	secure record (HbA1c levels, c-peptide levels, blood glucose levels)★	yes ★	Age, T1DM for 5 years, weight, BMI, c-peptide levels★	one primary diabetic complication ★	self report	yes, 1 year and 5 year post-transplant ★	Subjects withdraw from the trial unlikely to introduce bias ★	7.0
2007 Update on Allogeneic Islet Transplantation From the Collaborative Islet Transplant Registry (CITR). 2009. [19]	Somewhat representative of the average diabetic patients that underwent islet cells transplantation in the community ★	no description	secure record (HbA1c levels, c-peptide levels, blood glucose levels)★	yes ★	Age, T1DM for 5 years, weight, BMI, c-peptide levels★	not mentioned.	self report	yes, day 30, month 6, and 1 year post-transplant★	40% follow up loss★	6.0
Close N et al. 2007. [20]	Somewhat representative of the average diabetic patients that underwent islet cells transplantation in the community ★	no description	secure record (HbA1c levels, c-peptide levels)★	yes ★	Age, T1DM positive, weight, BMI★	not mentioned.	self report	yes, 6 months and 1 year post-transplant★	complete follow-up★	6.0
Bellin M et al. 2008. [22]	Somewhat representative of the average diabetic patients that underwent islet cells transplantation in the community ★	no description	secure record (HbA1c levels, c-peptide levels, insulin independence period)★	yes ★	Age, T1DM positive, weight, BMI★	hypoglycemic status, reduced awareness of hypoglycemia, creatinine clearance, anti-HLA antibody★	self report	yes, year 1, year 3, year >3 post-transplantation★	complete follow-up★	7.0
Ryan E et al. 2005. [23]	Somewhat representative of the average diabetic patients that underwent islet cells transplantation after severe continuous hypoglycemic episodes in the community ★	no description	secure record (HbA1c levels, c-peptide levels, hypoglycemic score and lability index)★	yes ★	Age, T1DM positive, weight, BMI★	problematic hypoglycemia ★	self report	yes, 5 years post-transplant★	complete follow-up★	7.0
Shapiro A et al. 2003. [24]	Somewhat representative of the average diabetic patients that underwent islet cells transplantation in the community ★	no description	secure record (HbA1c levels, c-peptide levels, insulin independence period)★	yes ★	Age, T1DM positive, weight, BMI★	not mentioned.	self report	yes, 1 year post-transplant★	complete follow-up★	6.0

Table 2: NOS Quality Assessment for Cohort Studies of Islet Cell Transplantation.

Study	Selection				Comparability		Outcome			Overall Score (/9.0)
	Representativeness	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration of outcome was not present at the start of study	Study controls for	Additional factors	Assessment of outcome	Follow-up	Adequacy of follow up	
Voltarelli J et al. 2009. [32]	Somewhat representative of the average newly diagnosed T1DM patients in the community ★	no description	secure record (insulin free period, c-peptide levels, HbA1c levels)★	yes ★	Age, newly diagnosed T1DM, weight★	positive antibodies against glutamic acid decarboxylase★	self report	yes, 7 to 36 months follow up post-transplant★	complete follow up★	6.0
Couri C et al. 2009. [33]	Somewhat representative of the average newly diagnosed T1DM patients in the community ★	no description	secure record (insulin free period, c-peptide levels, HbA1c levels)★	yes ★	Age, newly diagnosed T1DM, weight★	positive antibodies against glutamic acid decarboxylase★	self report	yes, 7 to 58 months follow up post-transplant★	complete follow up★	7.0
Zhang X et al. 2012. [34]	Somewhat representative of the average newly diagnosed T1DM patients in the community ★	no description	secure record (glucose levels, HbA1c, c-peptide levels, GAD antibody, insulin dosage)★	yes ★	age, newly diagnosed T1DM (within 6 months), hyperglycemic★	positive antibodies against glutamic acid decarboxylase★	self report	yes, 6 months follow up post-transplant★	complete follow up★	7.0
Xiang H et al. 2015. [35]	Somewhat representative of the average newly diagnosed T1DM patients in the community ★	no description	secure record (insulin free period, c-peptide, HbA1c, lipoprotein, TNF-alpha, IL-6, GAD)★	yes ★	age, BMI, initial daily insulin dose, newly diagnosed (not more than 6 weeks)★	positive antibodies against glutamic acid decarboxylase★	self report	yes, follow up of 28.5±8.3 months★	complete follow up★	7.0

Table 3: NOS Quality Assessment for Cohort Studies of Stem Cell Transplantation.

Study	Selection				Comparability		Outcome			Overall Score (/9.0)
	Adequate case definition	Representativeness	Selection of control	Definition of controls	Study controls for	Additional factors	Ascertainment of exposure	Same method for cases and controls	Non-response rate	
Yi G, et al. 2015. [36]	yes, based on self reports	consecutive or obviously representative series of cases★	hospital controls	28 patients with newly diagnosed T1DM at the same period of hospitalization★	newly diagnosed T1DM★	not mentioned	secure record (ketoacidosis onset, HbA1c, c-peptide levels, and insulin dosage)★	yes★	same rate for both groups★	6.0

Table 4: NOS for Case Control Studies of Stem Cell Transplantation.

MINORS for Case Series Studies

Study	Year	Clear aims	Inclusion of patients	Prospective data collection	Appropriate endpoints	Follow-up	Loss to follow up less than 5%	Prospective calculation of study size	Overall score (/16.0)
Markmann J et al. 2003. [25]	2003	2	2	2	1	2	0	1	10.0

Table 5: MINORS Quality Assessment for Islet Cell Transplantation Studies.

Study	Study Design	Sample size	Outcome Measure	Main Findings	
				Primary end point	Secondary endpoint
Islet Cell Transplantation studies					
Shapiro A et al. 2006. [18]	Prospective cohort study	36 patients (T1DM for 5 years)	Insulin independence: HbA1c levels, C-peptide levels, insulin-free period	44% of subjects were insulin independent after 1 year, 28% had partial function, and 28% had complete graft loss	76% required insulin, 31% remained insulin independent at 2 years
2007 Update on Allogeneic Islet Transplantation From the Collaborative Islet Transplant Registry (CITR). 2009. [19]	Prospective cohort study	315 patients (617 islet infusions)	primary: insulin independence (c-peptide, HbA1c, glucose levels) secondary: diagnosis or progression of diabetes complications	67% of the subjects were insulin independent at 2 years	12% of the subject were insulin independent after 4 years
Close N et al. 2007. [20]	Prospective cohort study	138 patients (266 islet infusions)	Insulin independence: HbA1c levels, C-peptide levels, insulin-free period	67% of the subjects were insulin independent at 6 months	58% were insulin independent at 12 months, 92% of the subject were protected from hypoglycemic episode
Brennan D et al. 2015. [21]	Prospective cohort study	7 patients	Insulin independence: HbA1c levels, C-peptide levels, insulin-free period, c-peptide to glucose ratio	all subjects demonstrated islet graft function for at least 10 years, all subjects were insulin independent for 54months post-transplant	2 subjects were insulin independent at 12 years of follow up
Bellin M et al. 2008. [22]	Prospective cohort study	6 patients (37 infusions)	Insulin independence: HbA1c levels, C-peptide levels, insulin-free period	5 subjects were insulin independent at 1 year	4 subjects were insulin independent at 3.4±0.4 years
Ryan E et al. 2005. [23]	Prospective cohort study	44 patients (128 infusions)	Insulin independence: HbA1c levels, C-peptide levels, insulin-free period, hypoglycemic score and lability index	all subjects demonstrated insulin independent post-transplant, 42% subject suffered from adverse events post-transplant	80% of subjects had c-peptide present, 10% were insulin independent at 5 years
Stem Cell Transplantation studies					
Soria B et al. 2000. [26]	In vivo experimental study	15 streptozotocin-induced diabetic mice	Plasma insulin levels, glucose levels.	Regulated insulin secretion is observed; Glycemic control of ES-transplanted diabetic mice is better than non-transplanted diabetic mice; transplanted mice corrected hyperglycemia within 1 week	Glycemic control of ES-transplanted diabetic mice is still not better than non-diabetic mice; transplanted mice restored body weight at 4 weeks
Sipione S et al. 2004. [27]	In vivo experimental study	12 streptozotocin-induced diabetic mice	Insulin production: c-peptide levels, glucose levels.	All the subjects had persisted hyperglycemia after the transplant; no significant effect on the life-span; small amount of insulin produced was not enough to reverse a severe hyperglycemia; teratomas were formed as adverse events.	proinsulin is synthesized in nestin(+)cells; the graft differentiated into insulin-producing cells but not beta cells; insulin production is not glucose-dependent; ES-derived cell contained 1000x less insulin than a mouse beta cell; cultures with neuronal features were proven to be unsuitable for T1DM.
Alipio Z et al. 2010. [28]	In vivo experimental study	30 streptozotocin-induced diabetic mice	Insulin production: c-peptide levels, glucose levels, HbA1c levels	All the subjects exhibited normal glucose levels (reversed diabetes) at 1 week post-transplant; iPS differentiated into insulin-producing cells in vivo	15 of the subjects were still alive and normoglycemic at 8 weeks post-transplant
Rezania A et al. 2012. [29]	In vivo experimental study	12 streptozotocin-induced diabetic mice; 3 mice in cohort 1, 4 mice in cohort 2, and 5 mice in cohort 3	Insulin production: c-peptide levels, glucose levels, HbA1c levels	All the subjects were glucose tolerant and insulin independent; maturation of stem cells into insulin-producing cells occurred in vivo; the cells produced insulin and glucagon; there was 4x increase circulating human c-peptide levels at 16 weeks post-transplant	All subjects were remained glucose tolerant; circulating c-peptide levels increased 10x at 10 weeks post-transplant; glucose tolerance was indistinguishable from non-diabetic mice at 34 weeks; development of hESCs mimicked human fetal pancreas; the safety and efficacy of this approach as a therapy for T1DM are warranted
Jurewicz M et al. 2010. [31]	In vivo experimental study	9 streptozotocin-induced diabetic mice	Insulin production: c-peptide levels, glucose levels. Cytokine profile: CD3 counts, T cell counts	83% of subjects treated using NOR MSCs efficiently reversed recent-onset T1DM; it suppressed diabetogenic immune cells and inflammatory agents	Congenetic MSCs transplant resulted in long term reversal of hyperglycemia and altered diabetogenic cytokine profile; ameliorated diabetes pathogenesis
Voltarelli J et al. 2009. [32]	Prospective cohort study	15 newly diagnosed T1DM patients	Insulin production: c-peptide levels, glucose levels, HbA1c levels, anti-glutamic acid decarboxylase antibody titers	14 subjects (93.3%) were insulin independent at 7-tp-36 months follow up (1 for 35 mo, 4 for 21 mo, 7 for 6 mo, 1 for 5 mo, and 1 for 1 month); c-peptide levels within normal range at 12 months	C-peptide levels was significantly greater at 24 months post-transplant; antibody levels decreased after 6 months, HbA1c levels were maintained in 13 patients; beta cell function was increased in 14 patients, prolonged insulin independence in majority of subjects.
Couri C et al. 2009. [33]	Prospective cohort study	23 newly diagnosed T1DM patients	Insulin production: c-peptide levels, glucose levels, HbA1c levels, anti-glutamic acid decarboxylase antibody titers	20 subjects (86.9%) were insulin independent at 30 months follow up; 8 patients relapsed	12 subjects (52%) maintained insulin independent at 52 months with HbA1c levels less than 7%, C-peptide increased significantly (p=0.001), and good glycemic control
Zhang X et al. 2012. [34]	Prospective cohort study	9 newly diagnosed T1DM patients	Insulin production: c-peptide levels, glucose levels, HbA1c levels, anti-glutamic acid decarboxylase antibody titers, insulin dosage	6 (67%) subjects were insulin independent post-transplant	6 subjects remained insulin independent at 6 months follow up with decreased GADA titer.
Xiang H et al. 2015. [35]	Retrospective cohort study	128 newly diagnosed T1DM patients	Insulin production: c-peptide levels, glucose levels, HbA1c levels	All subjects were insulin independent post-transplant	71 (55.4%) subjects were insulin independent at 18.5±8.3 months follow up
Yi G, et al. 2015. [36]	Case-control study	Case: 42 newly diagnosed T1DM patients; control: 28 newly diagnosed T1DM patients at the same period of hospitalization	ketoadicidosis on set, HbA1c levels, c-peptide leves, insulin dosage.	11 subjects from case group were still insulin dependent, 3 subjects (7.2%) were insulin independent for 2, 3, and 11 months respectively	HbA1c in the control group was lower than in case group at 3 years follow up

Table 6: Characteristics of Included Studies.

Outcome Measures

Study	Outcome					
	Longest insulin independence period	C-peptide Levels	HbA1c Levels	Infusions	Graft Function	Blood glucose levels
Islet Cell Transplantation						
Shapiro A et al. 2006. [18]	44% of subjects at 2 years (P=0.007)	70% of subjects had ≥ 0.3 ng/ml	Less than 6.5%	31% subjects received 1 infusion, 25% received 2 infusions, 44% received 3 infusions. 5000IE/kg for each infusions	44% of subjects completely functional; 28% partial function; 28% graft loss.	overnight fast <140mg/dL and 2 hour post-prandial <180mg/dL
2007 Update on Allogeneic Islet Transplantation From the Collaborative Islet Transplant Registry (CITR). 2009. [19]	12% of subjects were insulin independent at 4 years (P=0.004)	67% of subjects had ≥ 0.3 ng/ml	Average of $7.6 \pm 0.1\%$ (p=0.02), only 19% with less <6.5%	26% subjects received 1 infusion, 49% received 2 infusions, 21% three infusions, 1.6% received 4 infusions. 12,700 \pm 5,900 IE/kg.	40% completely functional at 1 month dropped to 12% at year 4; 18-22% of subjects were partial function; 20% of subjects had graft loss at 1 month post transplant increased to 70% at 4 year post-transplant.	Average of 172.8 ± 5.7 md/dL
Close N et al. 2007. [20]	58% of subjects were insulin independent at 1 year	N/A	Average of 7.6% (SD=1.3)	Total of 266 infusions	49.1% of subjects had functional graft, 13.4% of subjects had graft loss.	Fasting plasma glucose average of 169.8 mg/dL (SD=105.3) with 2.5% participants
Brennan D et al. 2015. [21]	85.7% of subjects were insulin independent at 11.6 years post-transplant; all subjects were insulin independent for 54 months	Median of 4.5ng/mL	Median of 6.3%	Total of 20 infusions for 7 subjects. 18,721 IE/kg.	All subjects had completely functional graft post-transplant, and 57% of subjects had partial function graft at the end of trial (12 years post-	Median glucose value 203 mg/dL
Bellin M et al. 2008. [22]	66.7% of subjects were insulin independent at 3.4 \pm 0.8 years	Average of 1.9 \pm 1.3 ng/mL	Average of 7.3 \pm 0.7%	Total of 11 infusions; 16.7% subjects received 1 infusion, 83.4% subjects received 2 infusions, average of 11,872 \pm 2541	83.3% of subjects had completely functional graft, while 16.7% of subjects had partial function graft	Mean fasting glucose level 106 \pm 17 mg/dL
Stem Cell Transplantation						
Voltaire III J et al. 2009. [32]	93% subjects were insulin independent at 36 months	Range from 0.3 ng/mL to 0.4 ng/mL	86.7% subjects had less than 7%	N/A	93% subjects had completely functional grafts (insulin independent)	within the normal range, <120mg/dL, and <140mg/dL post-prandial
Couri C et al. 2009. [33]	52% subjects were insulin independent at 31 months	Average of 90.3 ng/mL (p<0.001)	5.4%, 5.7%, 5.7%, 5.5%, 6% respectively at 3, 12, 24, 36, and 48 months	N/A	95% subjects had completely functional grafts (insulin independent)	Average of 398.6 mg/dL
Zhang X et al. 2012. [34]	67% of patients were insulin independent at	Average of 0.7% at 6 months, 0.61 ng/mL at 12 months	89% subjects maintained less than 7%, and 11% subjects were	N/A	67% subjects had completely functional grafts (insulin independent)	N/A
Xiang H et al. 2015. [35]	55.5% of subjects were insulin independent at 30 months	Average of 2.56 \pm 0.49 ng/mL in insulin independent subjects	Average of 7.21 \pm 2.64% in insulin independent subjects	N/A	55.5% subjects had completely functional grafts (insulin independent)	Average of 203.65 \pm 66.27 mg/dL in insulin independent subjects

Table 7: Outcome measures of islet cell transplantation and stem cell transplantation in cohort studies

Study	Outcome					
	Insulin Production	C-peptide Levels	HbA1c Levels	Blood glucose levels	Other Findings	Adverse effects
Soria B et al. 2000. [26]	insulin independent in vivo at 1 week	N/A	N/A	N/A	restore body weight in 4 weeks ; glycemic control of ES-transplanted diabetic mice is better than non-transplanted diabetic mice, but still not better than non-diabetic mice	N/A
Sipione S et al. 2004. [27]	Insulin secretion is not glucose dependent; ES-cell derived cultures contained 1000x less insulin than normal beta cells; transplantation did not correct diabetes; subjects remained hyperglycemic; death in 25 days post-transplant; small amount of insulin was produced without any significant impact	N/A	N/A	N/A	Constant growth of nestin-positive cells (25% of overall cell growth in culture); insulin-positive cells synthesized proinsulin;	Teratoma formation.
Alipio Z et al. 2010. [28]	β -like cells secreted insulin in response to glucose; corrected hyperglycemia in T1DM and T2DM; excellent glycemic control in 83% subjects at 1 week post-transplant; insulin level ranges fro 0.064 to 5.32 ng/L	N/A	40% lower than untreated diabetic mice, but still 2.4x higher than normal mice.	300mg/dL at week 4 without correction. After correction the blood glucose was maintained within normal range.	N/A	N/A
Rezania A et al. 2012. [29]	At week 25 post-transplant proinsulin secretion was not glucose-responsive; at 3 months the graft cells produced insulin, glucagon, and somatostatin and responsive towards glucose	At week 14 c-peptide was detected, and at 25 post-transplant c-peptide levels increased significantly (10x higher)= 2.89 \pm 0.51 ng/mL	N/A	At week 32-34 post-transplant the glucose levels between non-diabetic and transplanted mice were indistinguishable	N/A	N/A

Table 8: Outcome measures of stem cell transplantation in in vivo studies.

Outcome Measures	Yi G, et al. 2015. [36]			
	Case group	Control group	P-value	Interpretation
Insulin independence	67% of subjects were insulin independent for 2 to 6 months	N/A		N/A
C-peptide levels (ng/dL, mean±SD)	0.71±0.70 short term; 0.44±0.47 long term	0.54±0.61 short term; 0.35±0.35 long term	p>0.05	N/A
HbA1c levels (% , mean±SD)	8.39±1.48 short term; 8.56±1.44 long term	6.68±0.70 short term; 7.43±0.97 long term	p<0.01	HbA1c levels in the control group was much lower than that in case group at 3 to 5 years evaluation
Insulin dosage given (U/kg)	0.58±0.25 short term; 0.72±0.14 long term	0.46±0.19 short term; 0.77±0.25 long term	p>0.05	Insulin release were sufficient therefore subjects require less dosage after treatment to achieve stable glycemic control
Blood glucose levels	N/A	N/A	N/A	N/A
Main findings	Adverse reactions : gastrointestinal symptom eg. vomiting, diarrhea, weight and hair loss.			

Table 9: Outcome measures of stem cell transplantation in case control study [36].

Study	Outcome						
	Longest insulin independence period	C-peptide Levels	HbA1c Levels	Infusions	Graft Function	Antibody rejection (+/-)	Blood glucose levels
Markmann J et al. 2003. [25]	85.7% subjects were insulin independent at 9 months	Average of 3.3-4.0 ng/mL	N/A	9,000IE/kg delivered in 2 to 3 infusions for each subject	100% subjects were insulin independent post-transplant; 85% remained insulin independent	All patients were evaluated for panel reactive antibodies (PRA) and all patients had zero PRA	Ranges from 110-129 mg/dL

Table 10: Outcome measures of islet cell transplantation in case series study [25].

husbandry/housing of animals involved in the studies, and the funding source.

NOS for Cohort Studies [16]

Eleven cohort studies included in the review were assessed using NOS. More than half of the studies received the maximum stars of 7 out of 9, whereas the lowest score was 5 out of 9 [21].

Two quality assessment aspects were found to receive zero stars: in the selection aspect of assessment, all of the studies assessed did not provide information on the selection of non-exposed cohort, whereas in the outcome aspect of the quality assessment, all of the studies used self-report as the choice of assessment of outcome.

All the studies had the same level of representativeness, in which all of the studies were somewhat representative of the average diabetic patients seeking for transplantation in the community. The follow-up of cohort studies on both islet cell and stem cell transplantation varied from one year to 12 years post-transplantation, but all of the studies provided detailed information of the evaluation at one year post-transplantation, the study controls were also similar, which included age, T1DM positive, C-peptide levels, and BMI.

Characteristics of the Included Studies

The characteristics of the included studies are presented in details in Table 6.

Study design

Out of the 19 included studies, 10 were prospective cohort studies, one retrospective cohort studies by Xiang, et al. one case series study by Markmann, et al. one case-control study by Yi, et al. and six *in vivo* experimental studies [25,35,36].

Subject and Sample size

The detailed information on the sample size of included studies is presented in Table 6. Human subjects were involved in cohort studies, STZ-induced diabetic mice were involved in *in vivo* experimental studies.

Outcome measures

Outcome measures of included studies were varied, but all of the studies included insulin independence assessment of the patients. These included serum C-peptide levels, glycosylated hemoglobin (HbA1c) levels, insulin free period, and average blood glucose levels post-transplantation. A study by Yi, et al. also included exogenous insulin dosage needed, whereas Couri et al, Jurewicz,

et al. and Voltarelli, et al. included cytokine profile and antibody status as outcome measures.

Main findings

The main findings included the functionality evaluation of the graft post-transplantation, whether the patients were categorized as insulin independent, partial graft function, or graft loss.

Insulin Independence

Insulin independence period determines the ability of transplanted subjects with T1DM to maintain good glycemic control without exogenous insulin supply. Five studies of islet transplantation identified that 70-100% subjects were insulin independent at one year post-transplantation [18,20,21,22,24]. Shapiro, et al. CTR and Ryan, et al. reported that less than 50% remained insulin independent at 2, 4, and 5 years post-transplantation, respectively [18,19,23]. However, differing results were found in a more recent study. Brennan, et al. reported that 100% subjects were insulin independent at 4.5 years post-transplantation, 85.7% of subjects remained insulin independent at 11.6 years post-transplantation [21].

In the stem cell transplantation studies, all of included cohort studies reported that more than 50% subjects were insulin independent at one year post-transplantation [32-35]. Couri, et al. and Xiang, et al. reported that more than 50% of subjects were insulin independent at two years post-transplantation. Voltarelli, et al. has reported that 93% of subjects remained insulin independent at 3 years post-transplant, which is the longest insulin free period reported in the literature [32,33,35].

In vivo studies on stem cell transplantation have found that β -like cells secreted insulin in response to changes in glucose level that is when the glucose concentration in the circulation increases, insulin production also increases [28-30,21]. Soria, et al. demonstrated that subjects receiving embryonic stem cells (ESCs) transplantation had better glycemic control compared to diabetic subject that did not receive treatment, although the response was not as good as non-diabetic subjects [26]. A more recent study by Rezanian, et al. found that stem cells differentiated into pancreatic endocrine cells not only release insulin, but also glucagon and somatostatin [29]. This study also described that the glucose-responsive insulin release started to function at 3 months post-transplant [29]. In contrast, Sipione, et al. reported that embryonic stem (ES)-derived culture cells produced 1000x less insulin than normal β -cells which had no effect on reversing diabetes and death of STZ-induced diabetic mice at day 25 post-transplantation [27].

C-peptide Serum Levels

C-peptide serum levels can be used as a marker to determine the level of natural insulin produced by the body. C-peptide levels are not affected by exogenous insulin, meaning although the subjects can be given insulin therapy, the level of insulin being produced naturally by the body can still be measured. Six out of seven cohort studies investigating islet cell transplantation reported that participants had an average of C-peptide levels of \geq

0.3 ng/mL [18,19,21-24]. Shapiro, et al. demonstrated that 70% of total subjects with insulin independence or partial graft function had C-peptide level of \geq 0.3 ng/mL [18]. In a more recent study, Brennan, et al. reported the average of C-peptide levels of 4.5 ng/ml was the highest C-peptide level in post-transplant patients to date [21].

Four cohort studies and one case-control study of stem cell transplantation for T1DM showed that the average of C-peptide serum level was greater than 0.4 ng/mL, with the highest level reported being 2.56 ± 0.49 ng/mL [32-34]. In an *in vivo* study by Kroon, et al. the average C-peptide serum level was higher compared to the average of clinical studies [30].

HbA1c Levels

Glycated hemoglobin (HbA1c) levels can be used to identify the average plasma glucose concentration three months prior to when the measurement is taken. This testing is important to identify whether the level of blood glucose is constantly high/low or only transiently high/low. Four studies on islet transplantation have shown that the HbA1c levels measured during follow-up were less than 6.5% [18,21,23,24]. HbA1c level have been found to be lower in insulin independent subjects compared to subjects with partial graft function [23].

Alipio, et al. using STZ-induced diabetic mice, has reported that the number of HbA1c level was 40% lower compared to diabetic mice who received stem cell transplantation [28].

A supporting results were found in clinical trials where a study by Couri, et al. reported that the subjects had average HbA1c level less than 6%, while the other three studies revealed that the average HbA1c level were above 7% [32-35].

Blood Glucose Levels

According to five cohort studies, the average number of random blood glucose levels of subjects underwent islet transplantation ranges from 140 to 203 mg/dL [18,19,21,23,24]. There are four studies mentioned that the average random blood glucose level were below 200 mg/dL while an contradicting result was found in a recent study by Brennan, et al. Two studies by Close, et al. and Bellin, et al. revealed significantly different number of average fasting blood glucose level of 169.8 mg/dL and 106 mg/dL, respectively [18-24].

Two *in vivo* studies on stem cell transplantation for T1DM revealed that there was a significant correction of hyperglycemic condition at week 32-34 post-transplantation, in which the average random blood glucose of diabetic mice were below 200 mg/dL in both studies [28,30]. According to Rezanian, et al. the blood glucose level between diabetic mice and non-diabetic mice became indistinguishable at 32 weeks post-transplantation [29]. While in clinical trials, two studies suggested that the average blood glucose level were still above the recommendation range, with the highest number found on a study by Couri, et al. with the average of 398.6 mg/dL [33]. On the other hand, another study by Voltarelli, et al.

showed lower number, with the average of 140 mg/dL [32].

Discussion

Treatment options for T1DM have evolved in the past decade. Although the current standard treatment for T1DM is exogenous insulin therapy, the recent development of cellular-based therapy - such as islet cell and stem cell transplantation - offer very attractive options for permanent solution of T1DM. It provides better glycemic control, comfort, β -cells repairment, and insulin independence where the patient can live normally.

This systematic review aimed to compare between different cellular-based approaches for T1DM based on several parameters such as insulin independence (period, glucose-responsive insulin release), insulin and glucose level (C-peptide, blood glucose, and HbA1c level).

Quality Assessment of Included Studies

A total of 19 primary research studies published between January 2000 and November 2015 were included in this review. The included studies consist of seven cohort studies and one case series study about islet transplantation for T1DM, and six *in vivo* studies, four cohort studies, and one case-control study for stem cell transplantation. Studies with similar type showed similar outcome measures and subject characteristics, which allows for appropriate comparison between them. The author included different types of study due to limited amount of studies available. There is also a different stage of development between included studies. The studies on islet cell transplantation for T1DM are more developed compared to stem cell transplantation for T1DM, because there were more clinical trials published since the discovery of Edmonton Protocol in 2000 [10].

The included studies were assessed using NOS, ARRIVE and MINORS [15-17]. Six out of 11 cohort studies were considered to be of a high quality, and the remaining five were considered as moderate quality cohort studies. Only two out of six *in vivo* studies were considered to have high quality, while the remaining four were moderate quality experimental studies. The author also included one case-control study and one case-series study with moderate quality assessed using MINORS.

Outcome Measures

Insulin Independence

Twelve of the included studies evaluated the insulin independence (insulin-free) period of the subjects between treatments, and the results were quite conclusive. In terms of insulin-free period, islet cell transplantation has better outcomes, the period ranges from one year up to 12 years in human subjects, whereas the longest insulin-free period of stem cell transplantation in human subjects was three years. Even in three of the included studies by Shapiro, et al. and Brennan, et al. up to 100% subjects were insulin independent at one year post-transplantation, and 60% remained insulin independent after 2 years [18,21,22]. According to Bellin et al [22] the average of insulin independence in islet cell transplantation was 3.4 years which is still above the longest insulin-free period of

stem cell transplantation.

Although, we may say that islet cell transplantation currently has better chance to be considered as a standard therapy for T1DM, certain challenges hinders the widespread application of islet cell transplantation. The challenges includes limited β -cell source due to lack of donors available - the pancreas from brain dead donors (BDDs) are the current primary source of islets for transplantation - followed by poor islet engraftment, lack of oxygen and blood supply during the procedure, and auto- or allo-immunity post-transplantation [37]. Therefore, the stem cell transplantation is still considered as prospective treatment options that might replace islet cell transplantation in the future.

According to four of six *in vivo* studies included, the insulin secretion was glucose-responsive [28-31]. The amount of insulin being secreted is proportionally increased when the level of blood glucose increases. In addition, glucagon and somatostatin were released by the grafts as mentioned by Rezanian, et al., Jurewicz, et al. reported that congenic mesenchymal stem cells (NOR MSC) were able to suppress T-cell proliferation, correct hyperglycemia, and altered diabetogenic cytokine profile that reduced the autoimmune reaction towards β -cells [29,31]. The results of the included *in vivo* studies indicated a better prospect for a stable glycemic control, as well as recent-onset diabetes reversal in the future [26,28-31].

However, a contradicting result was also found in the study by Sipione, et al. in which the cells were immunoreactive towards C-peptide and were mostly apoptotic [27]. This was caused by the use of neurons and neuronal precursors as the main producers of insulin/proinsulin. Insulin was released but it was not glucose-responsive, therefore the study recommended other protocols. We may conclude that stem cells can differentiate into functional pancreatic endocrine cells, although not all type of stem cells can function in similar manner [26-31].

C-peptide Serum

C-peptide is connecting peptide of the proinsulin. It serves as a marker to determine the amount of insulin being naturally produced by the body [18]. The amount is directly proportional to the amount of insulin produced. Six out of seven studies on islet cell transplantation revealed that more than 60% of the subjects had C-peptide serum levels above 0.3 ng/mL ranges from 0.44 ng/mL to 4.5 ng/mL, which is considered to be high [18,19,21-25]. This proved that the graft was able to function properly, in which the cells naturally produced insulin into the circulation. Insulin would lower the glucose level in hyperglycemic condition. The higher the C-peptide serum level, the bigger the amount of insulin produced.

In vivo studies showed that the C-peptide production was glucose-stimulated, and started to be detected at 14 days post-transplantation [29,30]. This finding showed that the insulin was released in a basal-bolus post prandial physiologic pattern similar to normal individuals. When this occurs, diabetes in the subjects

is considered to have been reversed. Overall, the C-peptide levels between two treatments in all the included studies were within a similar range of 0.3 ng/mL to 4.5 ng/mL, which demonstrates that the proinsulin being produced by the body was about the same amount, variation might occur due to varied level of glucose levels in the circulation of the subjects, since the release of proinsulin was shown to be glucose-stimulated.

HbA1c Levels

Ryan, et al. reported that HbA1c levels in insulin independent subjects with completely functional grafts were lower compared to subjects included in the partial graft function and graft loss groups [23]. The reduced amount of HbA1c is caused by the presence of insulin produced by the transplanted cells. These results also served as proofs that the graft was functioning properly by constantly controlling glycemia through insulin production, in which it is depicted in a constant decrease of average blood glucose concentration. According to eight included cohort studies, the level of HbA1c were relatively higher in patients that underwent stem cell transplantation compared to patients that underwent islet cell transplantation [18,21,23-35,32-35]. However, the level of HbA1c found in stem cell transplantation patients were still relatively lower (40%) compared to subjects without treatment [32-35]. Although stem cell transplantation did not improve glycemic control as well as islet cell transplantation, it was still better than untreated diabetes.

Blood Glucose Levels

The National Institute for Health and Care Excellence (NICE) published a recommendation for blood glucose levels in both normal and diagnosing diabetes [38].

Plasma glucose test	Normal	Prediabetes	Diabetes
Random	Below 11.1 mmol/l Below 200 mg/dl	N/A	11.1 mmol/l or more 200 mg/dl or more
Fasting	Below 6.1 mmol/l Below 108 mg/dl	6.1 to 6.9 mmol/l 108 to 125 mg/dl	7.0 mmol/l or more 126 mg/dl or more
2 hour post-prandial	Below 7.8 mmol/l Below 140 mg/dl	7.8 to 11.0 mmol/l 140 to 199 mg/dl	11.1 mmol/l or more 200 mg/dl or more

Table 11: NICE blood glucose levels recommendation.

Six of seven cohort studies and one case series study on islet transplantation reported that the average of random blood glucose in the subjects were below 200 mg/dL, which is already within the plasma glucose level of normal population [18-20,22-24]. The studies reported that the graft was able to improve glycemic status of the diabetic subjects into constant level within the glucose level range in normal population.

Two *in vivo* studies by Alipio, et al. and Rezanian et al. stated that the glucose level became indistinguishable between non-diabetic and ES-transplanted STZ-induced diabetic mice at week 32-34 post-transplantation [28,29]. The ES-transplanted mice had an improved glycemic control due to properly functional grafts that produced insulin resulting in correction of hyperglycemia. The insulin production was capable to control the increased glucose level, while also maintaining concentration within the normal level. The results also proved that stem cell transplantation was able to reverse diabetes [26,28-31].

Limitations

General limitations

This review focuses on the cellular-based treatments for T1DM, which is believed to be the future solutions to better glycemic control compared to exogenous insulin supply as the current standard therapy. A comparison between islet cell transplantation and stem cell transplantation undoubtedly provide a more holistic management approach for T1DM. The different stage of study development between two treatments might account for the varied outcome measures, sample size, and type of studies available. Due to a limited amount of primary research studies had been conducted previously, a wide-range type of studies were added in the inclusion criteria, although it increases the risk of bias within and across studies, it reduces the risk of excluding potentially relevant studies.

Quality assessment

Different type of studies have different quality assessment tools which did not provide any exact quality threshold, therefore it was considered difficult to define whether a study was good or bad. However, it was possible to compare between studies using the criterias provided in the assessment guidelines in which a study can be relatively high/low compared to other studies by using the average points of included studies.

Outcome measures

Not all of the studies comprehensively evaluated all the outcome measures included in this review, therefore limited comparisons could be drawn. The different protocols used in each experimental studies and the pooling of results from studies using self-rated outcome measures might potentially affect the comprehensiveness and validity of the review. Also, the outcome measures were evaluated using different units in which standardization was necessary. Different subjects included in the study could also have effects on the study results, therefore comparisons were only conducted within the same studies.

Moreover, there are very limited numbers of studies that evaluate the effectiveness of stem cell transplantation in human subjects. Also, there have not been any comparative studies on the comparison between islet cell and stem cell transplantation for T1DM conducted before.

Implications

Since the current standard therapy, exogenous insulin supply, has been highly associated with poor glycemic control resulting in life-threatening hypoglycemic condition, cellular-based therapy was believed to be the attractive alternatives for T1DM [1,6,7,18]. Several potential benefits were found to be in favor for islet cell transplantation, as it was proven to have more evidence of success with longer insulin-independent period, and constant glycemic stability. It is relatively more developed in comparison with stem cell transplantation, and more preferred as the treatment of choice. However, stem cell transplantation also has promising prospects, as it tackled the problem with brain-dead pancreas donor shortage, since the sources are not limited to brain-dead donors but also

include living donors. Stem cell transplanted for T1DM also released insulin in glucose-stimulated manner that mimics the physiologic release of insulin in normal individuals. Although in the long run, both procedures were associated with high risk of adverse effects due to immunosuppressive regimen included in the protocols [9]. Therefore, the decision to implement one treatment over the other are depended on the condition of the patients, the physician's and patient's preferences.

Conclusion

Based on the results obtained from this review, we can conclude that islet stem cell transplantation has proven to have longer insulin-independent period compared to stem cell transplantation, although both treatments provided relatively better glycemic control compared to the current standard therapy, exogenous insulin therapy. The majority of the studies have reported that both treatments lead to a substantial improvement between pre-transplantation and post-transplantation periods. Although there was a limited amount of stem cell transplantation studies using human subjects, but based on the current available studies the results were quite conclusive.

Recommendations

Rigorous studies comparison between islet transplantation and stem cell transplantation for T1DM are warranted in order to determine which is most appropriate for treating T1DM. Future studies should be directed towards evaluating the occurrence of complication post-transplantation such as infection, cancer, or cardiovascular disease that may arise due to the procedures such as immunosuppressive regimen. In terms of effectiveness, future studies must employ standardized outcome measures to allow a more comprehensive analysis to be conducted in a collective manner. Future studies should also be encouraged to evaluate the different outcome measures comprehensively. The procedural details should also be specifically reported, especially in terms of the types of graft cells used, the application methods of both cell processing and transplantation. The future studies should also be directed into finding solutions for limited pancreas donor in islet cell transplantation, and increasing safety of stem cell transplantation by conducting more clinical trials.

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