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Article

Stem Cell Therapy in Treating Type 1 Diabetes Mellitus –Potential and Ethical Issues.

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Abstract— **Type 1 diabetes (T1D) is a deficiency in insulin production which is mainly due to loss of β-cell pancreatic islets. Patients with T1D need to be given exogenous insulin regularly. While improvements in the delivery of insulin and glucose monitoring methods have been effective in improving patient safety, insulin therapy is not a cure and is often associated with complications and debilitating hypoglycaemic episodes. Meanwhile, pancreas or islet transplantation as a gold standard only promises temporary freedom from exogenous insulin and suffers from issues of its own. Stem cell therapy may provide a more permanent solution, given stem cells' immunomodulatory characteristics and ability to self-renew and distinguish into specific cells. In this sense, the therapeutic potentials of stem cells are addressed in this study. These stem cells cover a wide range of treatments for T1D including embryonic stem cells, induced pluripotent stem cells, bone-marrow derived hematopoietic stem cells and multipotent mesenchymal stromal cells. The challenges faced by the current stem cell transplant in T1D treatment and Islamic viewpoints regarding ethics in stem cell research and therapy are also discussed. In conclusion, stem cell therapy offers a safe and efficient alternative treatment for T1D. However, besides the fatwa from Fatwa Committee of Selangor, the lack of Malaysian stem cells ethics should be further addressed.**

Keywords— **Stem cell therapy; type 1 diabetes; stem cell ethics.**

I. INTRODUCTION

Type 1 diabetes (T1D) is the most common type of diabetes mellitus among children and teenagers. The most recent incidence of T1D is 15 per 100,000 people and its prevalence was 9.5% worldwide [1]. T1D is characterised by insulin production deficiency. Patients with T1D need regular insulin administration to maintain their blood glucose levels in a normal range [2]. The main cause of T1D is β-cell pancreatic islet degradation resulting in extreme insulin deficiency with poor or untraceable C-peptide concentration. Two forms of T1D have been identified: type 1A and 1B. Type 1A arises from a cell-mediated autoimmune strike on β cells, while type 1B is much less common with no clear cause and occurs mainly among people of Asian or African origin with different degrees of insulin deficiency in intermittent ketoacidosis episodes [3].

T1D is a progressive condition that has numerous complications including retinopathy, nephropathy, neuropathy, and cardiovascular morbidity. Research studies have found that good glycaemic regulation leads to lower risk of complications of chronic diabetes early in the disease [2]. There are many approaches to regulate blood glucose levels physiologically, including exogenous insulin administration, medicines that reduce insulin resistance, whole pancreas transplant or replacing the β cell mass. One of the alternatives to replacing β cells is stem cell transplantation [4].

The recent definitive standard in treating T1D is the transplantation of the whole pancreas. This is due to the exhibited clinical viability. More than 50,000 pancreas transplantations have been performed since 1966 [5]. 90.5% of the recipients managed to survive for 4 years of post-transplant [6]. Meanwhile, the survival rate of the grafts for five and ten years were 55% and 50%. Insulin independence achieved over 3 years was 61% [7]. In this process, the immunosuppressive drugs are used extensively to prevent graft rejection [7]. Since it is a surgical procedure, the risks of having complications after the transplantation are still present. 10% of recipients experienced complications, including; thrombosis of the graft (4.9%), pancreatitis (1.9%), abdominal infections (1.2%), bleeding (0.6%) and leakage (0.3%) [8]. In addition, whole pancreas transplantation requires a single donor, but there is a restricted number of donors [7]. These consequences of pancreatic transplantation have paved the way for stem cell studies and therapy.

Stem cell research and therapy are relatively new in Malaysia, and have mostly included hematopoietic stem cells from bone marrow, peripheral blood and cord blood [9]. Stem cell therapy, also known as regenerative medicine, facilitates, the reconstruction of diseased, damaged or

wounded tissue by means of stem cells or their derivatives. In terms of blood related diseases or cancers, stem cell therapy has been used to treat leukemia [10], lymphoma [11], neuroblastoma [12] and multiple myeloma [13].

Stem cells are undifferentiated cells that can evolve into various cell and tissue types. The distinctive properties of stem cells include being unspecialized, having the ability to produce several different cell types, being able to divide and regenerate themselves over long periods of time and even being able to transform into specialized cells. A process known as differentiation will transform undifferentiated cells into specialized cells such as red blood cells [14], muscle cells [15] and even brain cells [16]. Numerous stem cells origins have been discovered by researchers, including embryonic stem cells (ESCs), adult somatic stem cells, induced pluripotent stem cells (iPSCs) and perinatal stem cells [17]. Stem cell laboratory experiments allow scientists to learn about the fundamental properties of the cells and what makes them distinct from other types of cells. However, the effectiveness and ethical considerations in the application of stem cell therapy as an alternative treatment in curing T1D remain in dispute. In this review, we summarise the potential source stem cells that are currently being studied for the treatment of T1D. Some ethical issues and Islamic points of view on the application of stem cell therapy are also addressed.

II. Types of Stem Cells Used for T1D Therapy

Stem cell therapy is a potential therapeutic tool for T1D. This stem cell therapy is the next level of transplantation, which uses cells instead of organs. These stem cells are able to induce the repair reflex of pathological or damaged cells as the results of regeneration and reconditioned of the cells. Currently, the protocol for stem cell differentiation focuses on the production of mature, single hormone-expressing, glucose-responsive human β cells that utilize data from pancreatic growth studies [18]. There are many special signals that participate in insulin-producing β cells programming to achieve stem cell differentiation. Examples include pancreas-specific transcription factor-1a (Ptf-1a), pancreatic and duodenal homeobox 1 (PDX-1), NK6 homeobox 1 (Nkx6.1), neurogenin-3 (Ngn-3) and mafA [19]. Understanding the prime factors involved in β-cell development has led to various approaches to acquiring β cells. Furthermore, a variety of stem cell models which have been used for differentiation of β cells *in vitro* such as embryonic stem cells, induced pluripotent stem cells, bone-marrow derived hematopoietic stem cells, and mesenchymal cells, as shown in table 1.

A. Embryonic stem cells

Embryonic stem cells originate from an undifferentiated inner mass cells of the human embryo. It is known for its potential to be pluripotent with unlimited replicating ability. Additionally, it has been shown that the transgenic expression of PDX-1 and Nkx6.1 stimulates the differentiation of ESCs into endocrine cells positive for insulin, somatostatin and glucagon expression [20]. Interestingly, the differentiation of ESCs by growth and extracellular-matrix factors like laminin, nicotinamide and insulin leads to the formation of ES-derived progeny that similar to the pancreatic lineage [21] thus replacing the pathologic cells. There are several studies have provided a definite proof in which the pancreatic cells derived from human embryonic stem cells could regulate hyperglycaemia to normoglycemic. For instance, human ESC-mature β cells encapsulated in alginate and transplanted into a diabetic mouse model induced by streptozotocin (STZ) resulted in successful glycaemic regulation for more than 100 days [22]. The necessity for immune suppression can be resolved by encapsulation of cells, which will help in securing these therapeutic tissues against host immune response [23]. The encapsulated cells displayed a minimum fibrosis level after 3 months of transplantation, with positive outcomes for human insulin and glucagon [22]. This shows that even with no involvement of immunosuppressive therapy, ESCs effectively resolved hyperglycaemia in the diabetic animals over a long period of time.

In another mice model, mice that efficiently underwent β -cell ablation were shown to regulate the blood glucose levels within the normal range compared to the mice with no grafted cells, which were unable to regulate their blood glucose levels [24]. Despite positive evidence from *in vivo* studies, the clinical application of ESCs have been hindered due to its teratogenic potential and ethical implications [25].

B. Induced pluripotent stem cells

Induced pluripotent stem cells can be obtained from blood cells and a few other cells. These cells are reprogrammed back in an embryonic pluripotent setting [26] that allows for unrestricted production of any sort of human cell desired for treatment. Human iPSCs have been found to be a reliable cell origin for the extraction of β-like cells which are glucose-responsive [27]. In an *in vivo* study, iPSCs were acquired from epithelial cells derived from the pancreas by reprogramming of non-obese diabetic (NOD) mouse. These cells were shown to distinguish into cells that produce insulin. Upon transplantation into diabetic mice, various β-cells marker of pancreas were expressed and hyperglycaemia was able to be normalized [28]. Another *in vivo* study by Jeon *et al.* also revealed that the level of serum insulin was higher (0.17 ± 0.008 ng/ml) in the post-transplantation of NOD mouse pancreas-derived epithelial cells (NPE-iPSC) compared to the control diabetic mice (~0.05 ± 0.01 ng/ml) [28].

The restoration of normal blood sugar in the hyperglycaemic mouse model is due to normal insulin production by pancreatic β-like cells generated from the induced pluripotent stem cells [29]. Interestingly, the level of blood sugar in streptozotocin (STZ)-treated mice was well-controlled in a normal range for up to 16 weeks after transplantation [29]. iPSCs obtained from the mice's fibroblast were used in the study, as this could lower the risk of graft rejection [29]. Additionally, iPSCs have limitless production capacity and this will help in generating more insulin-producing cells.

While iPSCs can be an adequate source for autologous β-cells, several barriers and challenges have hindered their actual clinical efficacy, including incomplete cell

maturations, chromosomal anomalies, tumour or oncogenic vulnerability and recurring T1D autoimmune attacks [30][31].

C. Bone-marrow derived hematopoietic stem cells

Bone-marrow derived hematopoietic stem cells (BM-HSCs) are cells that can form blood cells via the haematopoiesis process. For existing medical purposes, bone marrow cells are now regularly collected, and clinical collection guidelines have been established.

There have been numerous trials to test the effectiveness of autologous nonmyeloablative HSCs transplant on patients with T1D. Based on the reported studies, the best result of stem cell therapy with the longest period of insulin independent is BM-HSC. 58.9% of the patients were free from insulin for average period of 16 months and 7.53% of them have reduced their insulin demand by more than 50 percent. This might be due to granulocyte-colony stimulating factor (G-CSF) mobilizing $CD34^+$ BM-HSCs obtained from peripheral blood via leukapheresis [32]. G-CSF is utilized to activate endogenous stem cells in the BM-HSC. Leukapheresis is a laboratory technique that distinguishes white blood cells from a blood sample. One of the trials, the Polish Protocol, introduced plasmapheresis sessions to remove autoantibodies and immune complexes prior to the transplantation and prophylaxis of infection with oral diabetes medicines following transplantation [33]. After BM-HSCs transplantation, the average C-peptide level and HbA1c level in patients also remarkably improved in T1D patients. This might indicate that the use of $CD34^+$ BM-HSCs could offer significant effectiveness in treating T1D patients. However, such results are based on small trials and require validation through larger trials. Several unwanted complications post-BM-HSCs transplantation such as neutropenic fever and severe infections have also been reported (24).

D. Mesenchymal stem cells

Another source of tissue or 'adult' stem cells are mesenchymal stem cells (MSCs). MSCs are found in different body sections, including bone marrow, adipose tissue, umbilical cord blood, placenta and amniotic fluid [34]. Mesenchymal stem cells are also known of its pluripotency, self-regeneration and minimal antigenicity with low level of toxicity [18]. Furthermore, the cells are easily cultured and can be reproduced *in vitro*. In fact, the immunomodulatory and proangiogenic features make them suitable for combination therapeutic applications. Moreover, MSCs generate anti-inflammatory, immunosuppressive, chemokines and proangiogenic growth factors, while the immunomodulatory properties of MSCs is mediated via the cell-cell interactions. In an *in vivo* study, decreased in inflammatory activity was reported, leading to better sensitivity of insulin in the target tissues after umbilical cord-derived MSCs (UC-MSCs) injection on hyperglycaemic type 2 diabetic rats [18]. The latest analysis in a UC-MSC model found that after transplantation, MSC-derived IPCs were immunogenic.

Several trials have shown that bone marrow-derived MSCs (BM-MSCs) obtained from mice can evolve into insulin-producing cells (IPCs) expressing specific genes of pancreas [35]. The differentiation of BM-MSCs into IPCs could be further stimulated by the overexpression of PDX-1 in human BM-MSCs via genetic engineering [36]. As a result, the blood glucose levels in diabetic mice have decreased by transplantation of these differentiated IPCs cells. Ironically, patients injected with differentiated IPCs showed a 30% to 50% reduction in their insulin needs, whereby serum C-peptide levels improved 4 to 26 times [37]. However, because of some drawbacks, neither of these methods of differentiation are replicable for well-developed adult β cells.

TABLE I
COMPARISON OF WHOLE PANCREAS TRANSPLANT COMPAIRED TO STEM CELL THERAPIES IN T1D THERAPY.

Type of cells	Advantages	Disadvantages	Ref
Whole pancreas transplant	- Exhibited clinical viability	- Restricted number of donors - Expose to post-surgical risks - Required immunosuppression forever	[6] [7]
Embryonic stem cells	- Limitless production capacity - Has transgenic expression of PDX-1 and Nkx6.1	- Teratogenic potential - Ethical consequences	[22] [24]
Induced pluripotent stem cells	- Limitless production capacity, while preventing ethical concerns	- Incomplete cell maturations - Chromosomal anomalies - Tumor / oncogenic vulnerability - Recurring T1D autoimmune attacks	[28] [29]
Bone-marrow derived hematopoietic stem cells	- Regularly collected with clinical collection guidelines	- Vulnerable to complications such as neutropenic fever and systemic infections - Poor prognosis for T1D with diabetic ketoacidosis (DKA)	[32]
Mesenchymal stem cells	- Limitless production capacity - Minimal antigenicity with	- Contamination issue when produced in big quantities	[35] [37]

	low level of toxicity - Easily cultured - Produce anti-inflammatory, immunosuppressive, chemokines, proangiogenic growth factors.		

III. Limitations and Challenges in Stem Cell Transplant for T1D.

Stem cell therapy is a safer alternative in treating T1D compared to the transplantation of pancreas. This is because stem cell therapy is less invasive, safe and effective for selected patients with T1D [32]. However, there are some vulnerabilities which may occur in stem cell therapy such as the risk of developing tumours, abnormal chromosomes, immature insulin-producing cells or serious infection.

Therefore, it is advised that the use of ESCs and iPSCs be restricted because of the tumour vulnerability in humans [25][30][31]. Meanwhile, the use of BM-HSCs could lead to severe complications, and it is not a suitable therapy for T1D with DKA due to poor prognosis [32][33].

Xenogenic contamination issue is a major obstacle for iPSCs therapy in clinical applications due to the usage of mouse embryogenic fibroblast as a feeder layer. Thus, further research on biomaterials are done to be used as the feeder layer [38]. Interestingly, MSCs grown on biomaterials tend to specifically differentiate into chosen lineages of cells with an elasticity like the tissue of interest. Unfortunately, the differentiation fate of MSCs could not be directed to the mature differentiation stages as the differentiation only restricted to the early stages [38].

Immunosuppressant therapies accompanied by multiple complications may be required in patients undergoing stem cell therapy in order to prevent an immune attack [39]. Autoimmune attacks of T1D may reoccur post-transplant in certain stem cell therapy. The improvement in the technical part of the therapy process therefore needs to be considered. Perhaps the use of immunosuppressive regimens in lower dose and infection prophylactic could produce an effective therapy.

There have been major developments in stem cell research in many years. However, the randomization of clinical trials is complicated since most of the research and control groups rely on patients' willingness to undergo stem cell therapy. Hence, more randomized and controlled trials are required to confirm the promising reported outcomes of stem cell therapy [40].

IV. ethical Issues in Stem Cell Research and Therapy in Islamic Point of View

There are several ethical issues regarding the use of stem cell therapy especially ESCs. ESCs are obtained from discarded IVF embryos. In modern ethics, the use of ESCs for research purposes is allowed. However, the most important ethical issue here is getting the parental consent before collecting ESC samples. Meaning that, the use of placenta or umbilical cord blood stem cells is acceptable with the authorization of the parents if the foetus is aborted naturally or aborted for medical purposes. However, the use of spare embryos is considered less ethical compared to the derived-ESCs. Limited research has shown that a person's view of stem cell innovation is greatly influenced by their status and level of education and religion, as well as culture [41].

In Malaysia, ethics for stem cell therapy are detailed out in the Guideline for Stem Cell Research and Therapy (2009) [42]. The latest guideline for the stem cell therapy could be found in National Standards for Stem Cell Transplantation (2nd ed) that was published in 2018 [43]. However, there are still concerns on the ineffectiveness of this guideline in ensuring good ethical governance. Thus, the need for a new, revised Malaysian stem cell guideline and new regulatory policy has been noted by researchers [9].

In the context of Islam, the Muslim World League Fiqh Council promulgated a fatwa to allow researchers to use stem cells for medical purposes when their source is legitimate [44]. In addition, in Malaysia, the Fatwa Committee of Selangor has counselled that only surplus embryo can be used to carry out stem cell studies [45]. Moreover, Qur'anic verses and hadith have clearly stated that Allah disapproves a man who changes His creation. However, embryonic studies of stem cells do not alter Allah's creation but are part of an effort to cure patients from diseases [46].

In *maqasid shari'a*, Islam emphasizes the health of the body as a responsibility. Hence, stem cell therapy for medical purposes such as generating of certain cells to treat the impaired organ is a must [45]. Therefore, it becomes a responsibility (*fardhu kifayah*) if research into stem cells could alleviate the suffering of people from diseases.

Islam is a pure religion that provide the adherents with a broad path of life that covers all aspects of personal, social, moral, spiritual, political, cultural and many more [47]. Islamic law or *shari'a* governs Muslims' everyday lives. This includes modern biotechnology such as stem cell treatments. Through juristic preference or *istihsān*, one point of stem cell research is that it can cure different types of illnesses through its ability to differentiate into specific lineages of cells. Meanwhile, for *maslahah mursalah* from Imam Ghazali's criteria, the new act must be appropriate, effective, most probable and consistent with shari'a implementations.

V. Conclusions

There are four types of stem cells under trials used for T1D therapy: ESCs, iPSCs, BM-HSCs, and MSCs. Most trials have demonstrated promising results in regulating hyperglycemia, even with some adverse effects and limitations such as restricted donors. Even so, the advantages of stem cell therapy outweigh possible risks. Ultimately, despite Islamic ethical issues, which then resulted in conditional permission of the study and use of stem cells, there is a clear basis for further stem cell research for the sake of ummah. With further research and validation, such stem cell therapy might one day become a safe, efficient and permissible alternative treatment for T1D.

Thus, it is suggested that more clinical trials on T1D patients be carried out to develop more precise data and information.

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