

Therapies for Type 1 Diabetes Mellitus with Major Emphasis on Cell-based Therapies



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1. Introduction

Diabetes mellitus is one of the metabolic disorders characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion alone and or insulin action. The effects of diabetes mellitus are long-term damage, dysfunction, and failure of various organs. Some of the signs and symptoms of diabetes mellitus are increased thirst and hunger, frequent urination, blurred vision, frequent infections such as skin and vaginal, etc.

There are main two types of diabetes mellitus including insulin-dependent or juvenile diabetes or type 1 diabetes mellitus (T1DM) and insulin-independent or adult-onset or type 2 diabetes mellitus. T1DM is the most prevalent chronic autoimmune ailment characterized by a lack of insulin secretion due to pancreatic β -cells damage that results in hyperglycemia. Globally, around 8.4 million individuals were reported to be affected by T1DM, of which 18% (1.5 million) were younger under the age of 20 years, 64% (5.4 million) were between the age of 20–59 years, and 19% (1.6 million) were of 60 years or older (1). The International Diabetes Federation predicted the prevalence of T1DM as 643 million by 2030 and 783 million by 2045 (2).

The different kinds of treatment strategies including insulin replacement therapy, transplantation therapy, and cell-based therapies are reported for the management of T1DM. Recently, advanced cell-based therapies are found to be promising for the effective management of T1DM.

2. Treatment approaches for type 1 diabetes mellitus and associated challenges

Diabetes devoid of suitable treatment can cause various acute (diabetic ketoacidosis, hypoglycemia) and chronic (diabetic retinopathy, diabetic nephropathy, and cardiovascular disease) complications (3). The cost of diabetes treatment is anticipated to increase significantly by 2030 across various corners of the globe including low and middle-income countries (4). The different types of treatment strategies used for T1DM are clinical evidence-based and cell-based therapies (Figure 1).

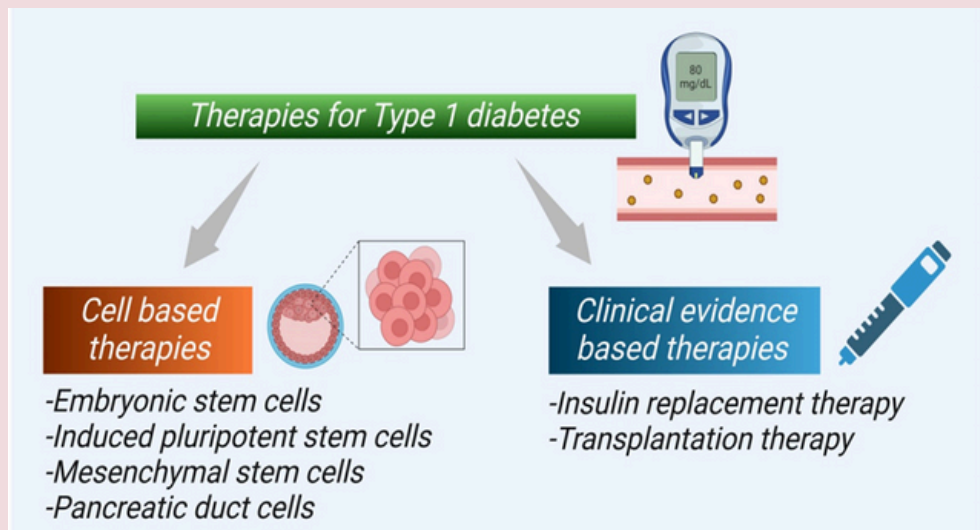


Figure 1: Different treatment strategies for type 1 diabetes mellitus

2.1. Insulin replacement therapy

T1DM is mainly associated with complete loss of insulin due to the damage of pancreatic β -cells. Inadequate islet cell repair processes are another issue that eventually compromises glycemic control. Thus, insulin replacement is a first-line therapy for T1DM. Various short and long-acting insulin preparations are widely used. However, hypoglycemia is a serious side effect associated with this therapy that can cause tachycardia, cardiac arrhythmias, sweating, coma, and death. In addition, other bottlenecks associated with insulin replacement therapy are invasive procedures, weight gain, dermatological reactions, hypersensitivity (systemic or local), and gastrointestinal distress (5). The use of artificial pancreas is also approved by Food and Drug Administration (FDA). However, excessive cost of equipment and sensor, scar tissue formation by frequent micro-needle insertion, and early sensor failure are chief drawbacks of this approach (6). Nowadays, the applicability of this therapy is enhanced via self-glucose monitoring devices and a new method of administering oral insulin using a self-orienting millimeter-scale applicator (7).

2.2. Transplantation therapy

Recently, transplantation of the pancreas and islet has shown great promise in the treatment of T1DM by restoring the normal regulation of blood glucose. However, the risk of chronic pancreatitis in pediatrics is a chief challenge associated with transplantation therapy. The clinical applications of these therapies have also been limited owing to the scarcity of pancreas and islets obtained from human organ donors, transplantation-related difficulties, huge costs, and inadequate procedural accessibility. Moreover, infusion methods of islet transplantation may cause portal vein thrombosis or intraperitoneal bleeding and some interim immunosuppression troubles (5).

2.3. Cell-based therapies

Cell-based therapies such as stem cell-based therapies have shown great potential in the management of T1DM successfully by overcoming the drawbacks of the aforesaid approaches. Stem cells serve as a potential source of providing glucose-responsive insulin-producing β -cells continuously and it also has the capacity to increase the survival and functionality of transplanted islets.

2.3.1. Human embryonic stem cells (hESCs)

The hESCs produce somatic cells in a developing embryo. These hESCs can be employed to develop new β -cells for transplantation into T1DM patients. Nowadays, it is very simple to differentiate between the insulin-producing β -cell, endocrine progenitor, and pancreatic progenitor via forced expression of pancreatic transcription factors. Thus, this strategy can be efficient to develop insulin-producing β -cells (8-9). In the United States, the phase 2 trial study is undergoing to evaluate the effect of pancreatic progenitors derived from hESCs in T1DM patients (NCT02239354). In another interesting study, Gopika et al., have developed mature β -cells from hESCs in vitro and transplanted them into diabetic mice. They observed a significant increase in metabolic activity, structural maturation of mitochondria, and a substantial decrease in hyperglycemia in diabetic mice in vivo following transplantation of matured β -cells (10).

2.3.2. Induced pluripotent stem cells (iPSC)

These cells are generated from somatic cells. The development of autologous iPSC technology has shown the capability to separate several patient-specific iPSCs from adult somatic cells into functional β -cells. These iPSC exhibited characteristics similar to embryonic stem cells and similar pluripotent features also. Alipio and co-workers investigated the potential of pancreatic β -cells derived from iPSC in a diabetic mouse. The transplantation of iPSC caused the generation of β like cells which secreted insulin in response to glucose and corrected hyperglycemic phenotype in mouse models. Thus, the obtained outcomes revealed the clinical potential of reprogrammed somatic cells using iPSC in the treatment of diabetes T1DM (11).

2.3.3. Mesenchymal stem cells (MSCs)

MSCs are the most generally used cell-based therapy in T1DM due to their diverse sources, simple isolation process, low immunogenicity, and self-regenerative capacity (12). Moreover, MSCs-based therapy has become incredibly popular in the treatment of T1DM owing to its capacity to control fibrosis, tissue generation, and modify immune response (13). El-Sawah et al., investigated the effect of MSCs on diabetic rats. They noticed a significant increase in the insulin and C-peptide level in serum thereby a decrease in hyperglycemia following treatment with MSCs. Additionally, MSCs caused a significant decrease in the serum level of kidney and liver function markers in diabetic rats, revealing their renal-hepato defensive benefits in T1DM (14). Thus, better effectiveness was observed with MSCs against T1DM with no sign of an adverse effect.

2.3.4. Pancreatic duct cells

The exocrine cell compartment of the pancreas is composed of acinar and duct cells. It is reported that functional insulin-producing cells can be developed using rat exocrine tissue in vitro via transdifferentiation approach by the addition of epidermal growth factor and leukemia inhibiting factor to the media. The insulin-producing pancreatic duct cells developed via this approach can be useful in the efficient treatment of T1DM (15). For instance, Okuno and co-workers investigated the potential of these pancreatic duct cells obtained by the transdifferentiation process in diabetic rodents. They concluded pancreatic duct cells as a promising source of autologous transplantable insulin-secreting cells for the treatment of T1DM (16).

3. Conclusion

T1DM remains the foremost cause of kidney failure, blindness, and stroke. T1DM patient's life quality has improved with various fast- and long-acting insulin analogues, but there are still many obstacles to overcome. The huge cost and immunosuppression have limited the applications of transplantation therapy. Stem cell-based therapy has emerged as an advanced approach to the treatment of T1DM. However, the clinical trial outcomes of this approach are still lacking and a lot of issues and technological challenges need to be addressed.

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