



# Stem cell therapy emerging as the key player in treating type 1 diabetes mellitus

ARUNA V. VANIKAR<sup>1,2</sup>, HARGOVIND L. TRIVEDI<sup>1,3</sup> & UMANG G. THAKKAR<sup>1</sup>

<sup>1</sup>Department of Regenerative Medicine and Stem Cell Therapy, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre, Dr. H.L. Trivedi Institute of Transplantation Sciences, Gujarat, India, <sup>2</sup>Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre, Dr. H.L. Trivedi Institute of Transplantation Sciences, Gujarat, India, and <sup>3</sup>Department of Nephrology and Transplantation Medicine, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre, Dr. H.L. Trivedi Institute of Transplantation Sciences, Gujarat, India

## Abstract

Type 1 diabetes mellitus (T1DM) is an autoimmune disease causing progressive destruction of pancreatic  $\beta$  cells, ultimately resulting in loss of insulin secretion producing hyperglycemia usually affecting children. Replacement of damaged  $\beta$  cells by cell therapy can treat it. Currently available strategies are insulin replacement and islet/pancreas transplantation. Unfortunately these offer rescue for variable duration due to development of autoantibodies. For pancreas/islet transplantation a deceased donor is required and various shortfalls of treatment include quantum, cumbersome technique, immune rejection and limited availability of donors. Stem cell therapy with assistance of cellular reprogramming and  $\beta$ -cell regeneration can open up new therapeutic modalities. The present review describes the history and current knowledge of T1DM, evolution of cell therapies and different cellular therapies to cure this condition.

**Key Words:** *adult stem cells, induced pluripotent stem cells, insulin-secreting cells, type 1 diabetes mellitus, stem cell therapy, mesenchymal stromal cells*

## Introduction

Type 1 diabetes mellitus (T1DM) is a chronic multifactorial autoimmune, idiopathic or genetic disorder of the pancreas causing progressive destruction of insulin secreting  $\beta$  cells. It is the disease of children and adolescents, usually noticed for the first time around the age of 5–7 years. The typical symptoms are polydipsia, polyuria and polyphagia with overt hyperglycemia [1]. Males are more frequently affected than females [2]. The disease is believed to be autoimmune in nature and triggered by several factors like seasons of autumn and winter, viral/bacterial infections and environmental pollutants [3–5]. The prevalence of T1DM is 0.1–0.5% in the general population and the incidence is 30–50/100,000 persons [6–12]. The disease is increasing at an alarming rate of 3% every year. It eventually causes multi-organ dysfunction like diabetic retinopathy, ketoacidosis, nephropathy, neuropathy, hypercoagulability, cardiovascular diseases and even end-stage organ failure.

Insulin replacement therapy is the only well-known and accepted therapeutic modality currently.

## Diagnostic criteria for T1DM and trials for cure

T1DM has been classified by the American Diabetes Association and the World Health Organization (WHO) Expert Committee on diabetes mellitus (DM) as immune mediated and idiopathic [13]. Low levels of serum C-peptide remain the constant reliable diagnostic indicator of T1DM. Blood sugar and glycosylated hemoglobin (HbA1c) levels are used to decide the diabetic status of the patient. For establishing T1DM, apart from blood sugars and low serum C-peptide levels, people with markers of autoimmunity are antibodies to  $\beta$  cells, glutamic acid decarboxylase (GAD), islet cells, protein tyrosine phosphatase like Ia2 or ICA512. HLA-DR3/4 and DQ8 genotypes are believed to be prone to develop T1DM. Histopathology of islets has shown insulinitis in early

Correspondence: **Aruna V. Vanikar**, MD, PhD, Department of Pathology, Laboratory Medicine, Transfusion Services and Immunohematology; Department of Regenerative Medicine and Stem Cell Therapy, G.R. Doshi and K.M. Mehta Institute of Kidney Diseases & Research Centre, Dr. H.L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad 380016, Gujarat, India. E-mail: [vanikararuna@yahoo.com](mailto:vanikararuna@yahoo.com)

(Received 21 April 2016; accepted 7 June 2016)

stages and later on chronic irreversible changes of  $\beta$ -cell depletion, atrophy and fibrosis.

With the increase in prevalence of T1DM and its wide-spread ill effects, interest in understanding the etio-pathogenesis and cure of T1DM are increasing the world over [14].

The new treatment goals are preserving C-peptide production or returning to normalization and establishing a mechanism to control or block autoimmune destruction of insulin-secreting  $\beta$  cells. Phase 3 trials of anti-CD3 antibodies (Otelixizumab) on children with recently detected T1DM and Diamyd vaccine (GAD-alum immunotherapy) did not meet with primary end points [15–21]. Administration of a synthetic immune-modulator “DiaPep277” in adults with T1DM at 3-month intervals led to stable levels of stimulated C-peptide concentrations with slow decrease at 1 year [22,23]. However, immune modulators failed to show durable effects. A fusion protein CTLA4-immunoglobulin (Ig; abatacept) preserved stimulated C-peptide concentration for only 9 months despite continuous intravenous administration for 2 years [18]. These results imply that single-agent immunosuppression alone might be insufficient to completely control the autoimmune destruction of  $\beta$  cells, or that more specific and targeted therapies are needed.

### Glucose homeostasis and insulin secretion

Glucose homeostasis requires finely regulated insulin secretion by pancreatic  $\beta$  cells in islets of Langerhans [24]. Under fasting basal conditions, insulin is secreted at the rate of about 2 pmol/kg/min and after meals this rate increases by about 5- to 10-fold [25–27]. To accomplish this requires normally functioning  $\beta$  cells in a sufficient number, collectively referred to as  $\beta$ -cell mass. In health, the human pancreas contains approximately one million islets, each containing approximately two thousand  $\beta$  cells [28–31]. Thus, the  $\beta$  cells constitute approximately 1.5% of the total pancreatic mass of 1–2 g [32]. A single  $\beta$  cell with a size of 15  $\mu$ m can store about 10,000 insulin granules and a single insulin granule the size of 300 nm contains approximately 200,000 molecules of the crystallized insulin [33]. This is a well-orchestrated process, which is initially triggered by the glucose intake at the cell membrane and then eventually ends up with the glucose-responding insulin secretion [34]. The generation of reliable pancreatic  $\beta$  cells is a difficult task. Instead a combined approach to block the destructive pathways and improve  $\beta$ -cell viability to preserve endogenous insulin production would be a plausible approach (Figure 1).

Normal blood sugar in fasting state is maintained between 70 and 126 mg/dL and post-prandial blood sugar measured 2 h after meals is 110–140 mg/dL. When random blood sugar is more than 200 mg/dL,

a symptomatic individual is suspected to have developed DM. Subsequent different investigations include oral glucose tolerance test to confirm blood sugar of  $\geq 200$  mg/dL at 2 h after taking 75 g oral glucose and HbA1c  $\geq 6.5\%$ , which establishes DM. T1DM is usually differentiated from T2DM by low serum C-peptide level.

### Immune intervention in T1DM

In 1981, Elliot *et al.* treated children newly diagnosed with T1DM with prednisone with the aim of stopping pancreatic  $\beta$ -cell destruction by the autoimmune process. These children showed improvement in urinary C-peptide for 1 year [35,36]. Subsequently, different trials were conducted using azathioprine, azathioprine plus prednisone and cyclosporine [37–39]. There was variable beneficial response in all of these trials for periods ranging from weeks to months in the form of partial preservation of  $\beta$ -cell mass and maintenance of C-peptide levels. However, the toxicity due to these interventions made them unpopular. Thus searching for alternative approaches began.

### Pancreas and islet transplantation

The first pancreatic transplantation was performed by Kelly *et al.* in 1966 to treat T1DM and after that more than 25,000 pancreatic transplantations have been conducted worldwide [40–42]. Rapid control of hyperglycemia with consequential discontinuation of the exogenous insulin supplementation was noted in successful cases. However, the major drawbacks were significant morbidity related to major surgery and requirement of life-long immunosuppression, which had its own side effects including recurrence of diabetes [43]. These drawbacks directed the scientists to work on other paths. Ricordi *et al.* and scientists at Edmonton developed techniques of islet extraction and transplantation to cure T1DM [44,45]. However, these protocols could not succeed in rendering insulin-free survival for more than 5 years [46]. Other modalities of encapsulation, immune modulation and delivery techniques are still being developed, however, success is still far on the horizon [47].

### Alternative approach to islet/pancreas transplantation: stem cell therapy

The need for unlimited supply of a substitute for insulin-secreting  $\beta$  cells led to research on the suitability of stem or progenitor cells to generate insulin-secreting cells (ISC). The main objectives of these cell-based therapies was to down-regulate the immune system and abrogate or at least halt the process of autoimmune destruction of these cells. The other aim was to generate stem cells (SCs) and differentiate them in to functional insulin-secreting  $\beta$  cell/ $\beta$ -like cells to

Download English Version:

<https://daneshyari.com/en/article/2171005>

Download Persian Version:

<https://daneshyari.com/article/2171005>

[Daneshyari.com](https://daneshyari.com)