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Clinical efficacy of autologous stem cell transplantation for the treatment of patients with type 2 diabetes mellitus: a meta-analysis

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Abstract

Background aims. In this study, we investigate whether bone marrow mononuclear cells (BM-MNC) or peripheral blood mononuclear cells (PB-MNC) have therapeutic efficacy in type 2 diabetes (T2D). *Methods.* Search terms included stem cell, bone marrow cell, peripheral blood cell, umbilical cord blood and T2D in MEDLINE, the Cochrane Controlled Trials Register, EMBASE, the Wanfang Database, the China Science and Technology Periodical Database and China Journal Net. *Results.* Fifteen trials met our inclusion criteria ($n = 497$). One group included 266 cases with BM-MNC therapy and the other group contained 231 cases with PB-MNC treatment. Glycosylated hemoglobin was decreased after BM-MNC or PB-MNC therapy compared with that before (12 months: $P < 0.001$; 6 months: $P < 0.001$; 3 months: $P < 0.05$). Fasting plasma glucose was reduced in BM-MNC therapy group compared with control after 12-month follow-up ($P < 0.001$) and after BM-MNC therapy compared with that before (9 months: $P < 0.001$) but was not obvious in other stages. Meanwhile, the analysis showed that C-peptide level increased after BM-MNC and PB-MNC therapy compared with the control therapy (12 months: $P < 0.001$) and with that before therapy (6 months: $P < 0.05$). Insulin requirement reduction was also observed in patients receiving BM-MNC therapy (3, 6, 9 and 12 months: $P < 0.05$). *Conclusions.* To a certain extent, BM-MNC or PB-MNC therapy for T2D demonstrated superiority of glycemic control, increased insulin biosynthesis and elevated insulin secretion from existing β-cells and might prevent islet cell loss.

Key Words: *bone marrow mononuclear cell, meta-analysis, peripheral blood mononuclear cell, stem cell, type 2 diabetes mellitus*

Introduction

The global prevalence of diabetes in 2012 was estimated to be more than 10% among adults. According to the report of the World Health Organization, the total number of patients with diabetes is projected to reach 366 million in 2030. Of the diabetic population, 95% are of type 2, characterized by two defects, namely progressive and inexorable β-cell dysfunction, which superimposed on insulin secretion and sensitivity [1–3]. Diabetes can result in multi-system chronic complications, particularly micro- and macro-vascular complications, with high morbidity and mortality rates. Chronic hyperglycemia can also damage the eyes, kidneys, nerves, heart and blood vessels. Once a person is diagnosed with diabetes mellitus, they will generally need to take drugs or insulin all their life, which can cause a great deal of disruption to their work and life in general [3].

Recently, research has focused on stem cells to generate functional β cells [4]. In addition to primary pancreatic β cells, studies on regeneration of functional insulin producing cells suggested various alternative cell sources including embryonic stem cells, induced pluripotent stem cells and adult stem cells, for example, bone marrow cells (BMCs) or bone marrow mononuclear cells (BM-MNC), which mainly contain mesenchymal stromal cells (MSCs) and hemopoietic stem cells, peripheral blood mononuclear cells (PB-MNC), umbilical cord blood stem cells (UCB), pancreatic stem cells and hepatic stem cells. In addition, the conversion of the gall bladder, skin fibroblasts, blastocyst-derived hypoblast stem cell–like cells and induced pluripotent stem cells into insulin-secreting cells has been tested [5–8]. Among them, MSCs were demonstrated to inhibit T-cell–mediated immune responses against newly formed β cells, which, in turn, are able to survive in this altered immunological milieu [9]. As a new therapeutic agent, MSCs in the treatment of diabetic cardiomyopathy, diabetic nephropathy, diabetic polyneuropathy, diabetic retinopathy and

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diabetic wounds were applied [10,11]. Prochymal, a human MSC—based stem cell therapy has been designated by the US Food and Drug Administration for the treatment of acute graft-versus-host disease and for ischemic diseases, neurologic disorders and diabetes, among others [12].

Stem cell therapy offers a new paradigm in the management of T2D after its success in an elegant study by Voltarelli *et al.* [13] in patients with type 1 diabetes mellitus (T1DM). Phase I/II clinical trials of intra-arterial pancreatic infusion of total autologous BM and/or BM-derived stem cells are currently under way, applying for the treatment of T2D at Fuzhou General Hospital in China (in combination with hyperbaric oxygen therapy; NCT00767260), at Postgraduate Institute of Medical Education and Research in India (NCT00644241), at Shan-dong University in China (NCT00465478), at the University of Illinois at Chicago (NCT01415726) and at the University of Miami (NCT01786707). A total number of 88 registered clinical trials on T2D in phase I/II can be found on the website for clinicaltrials.gov (http://www.clinicals.gov) with the key word of "stem cell" and "type 2 diabetes" until August 31, 2014. There have been some trials reporting that stem cell therapy can control patients' hyperglycemia and improve the function of pancreatic islets [14].We herein performed a systematic review and meta-analysis of clinical trials to assess the efficacy and tolerability of stem cells in the treatment of patients with T2D. The aim of this Review was to evaluate the impact of stem cell—based therapy on the clinical response and clinical observation results as well as to assess the efficacy of such a treatment by glycosylated hemoglobin (HbA1c), C-peptide, fasting plasma glucose (FPG) and insulin requirement.

Methods

Search strategy and selection criteria

Trials were identified by electronic search in the PubMed database (1976 onward), Embase (1966 onward), the Cochrane Central Registry of Controlled Trials (no date restriction), the Wanfang Database (no date restriction), the China Science and Technology Periodical Database (no date restriction), China Journal Net (no date restriction), reference lists of published trials and relevant review articles. The search strategy included the medical subject headings of "diabetes," "stem cells," "type 2 diabetes," "mesenchymal stem cell," "cell therapy," "bone marrow mononuclear cell," "peripheral blood mononuclear cell" and "beta cell" for the full text search. The type of the study design (ie, whether the trial reported the mode of randomization, allocation concealment, description of withdrawals per arm and blinding) for all of the trials included in the study and the respective study duration was demonstrated by the corresponding end point. No language limits were applied. The initial search was performed in November of 2012, with updates in July 2014. Furthermore, we consulted with experts in this field and performed manual searches in reference lists. We also searched http://www.ClinicalTrials.gov website for the information of prospective and ongoing trials. We excluded abstracts that were never subsequently published as full papers and studies on animals.

Data extraction and quality assessment

Data extraction was independently conducted by two authors with the use of a standardized approach. Disagreement was adjudicated by a third author after referring back to the original publications. We collected the trial data including authors' names, journal, year of publication, sample size per arm, regimen used, median or mean age of patients, sex, history of T2D, HbA1c, C-peptide, FPG, insulin requirement of patients and information pertaining to study design in our meta-analysis.

Definition of outcome measures

HbA1c is a measure of the degree to which hemoglobin is glycosylated in erythrocytes and is expressed as a percentage of total hemoglobin concentration. It reflects the exposure of erythrocytes to glucose in an irreversible and time- and concentration-dependent manner and is also determined by the FPG assessment. The secondary object was the C-peptide level and insulin requirement that denote the function of pancreatic islets.

Statistical analysis

The analysis was carried out by means of pair-wise comparison of the stem cell containing arms of the identified trials with the respective non—stem cell arms and also the comparison before and after the stem cell therapy. Treatment effects are reflected by HbA1c, FPG, C-peptide and insulin requirement. The data of HbA1c, FPG, C-peptide and insulin requirement in each arm were extracted from each trial and combined by use of a method by Mantel and Haenszel (Review Manager Version 5.0, Nordic Cochran Centre). To evaluate whether the results of the studies were homogeneous, we used Cochran's Q test; it is a χ^2 test with degrees of freedom equal to the number of studies minus 1 and tests the null hypothesis that the difference between the study