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Efficacy of mesenchymal stem cell therapy on glucose levels in type 2 diabetes mellitus: A systematic review and meta-analysis

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ABSTRACT

Aims/Introduction: In recent years, mesenchymal cellular therapies have received much attention in the treatment of diabetes. In this meta-analysis, we aimed to evaluate the efficacy of mesenchymal stem cell therapy in type 2 diabetes mellitus patients.

Materials and Methods: A comprehensive literature search was carried out using PubMed, Scopus, Web of Science and Central databases. A total of 1,721 articles were identified, from which nine full-text clinical trials were qualified to enter the current meta-analysis. The assessment groups included patients with type 2 diabetes, and levels of C-peptide, glycosylated hemoglobin and insulin dose were analyzed before and after mesenchymal stem cell infusion. Data analysis was carried out in Stata version 11, and the Jadad Score Scale was applied for quality assessment.

Results: Changes in levels of C-peptide after mesenchymal stem cell therapy were: standardized mean difference 0.20, 95% confidence interval −0.61 to 1.00, glycosylated hemoglobin levels were: standardized mean difference −1.45, 95% confidence interval −2.10 to −0.79 and insulin dose were: standardized mean difference −1.40, 95% confidence interval −2.88 to 0.09.

Conclusions: This meta-analysis of prospective studies showed associations between mesenchymal stem cell therapy and control of glucose level in patients with type 2 diabetes.

INTRODUCTION

Diabetes mellitus is a major disease that is on the rise worldwide[1,2]. In this disease, insulin resistance or defects in insulin secretion lead to a metabolic disorder caused by hyperglycemia[2,3]. The disease is divided into two subgroups: type 1 diabetes and type 2 diabetes[4]. Type 1 diabetes is characterized by insulin secretory defect, whereas in type 2 diabetes, insulin resistance is observed in patients[5,6]

Genetic and environmental factors play major roles in the development of diabetes mellitus, although the latter is found to be more common[7]. Until today, there is no cure available for diabetes, but insulin injections and oral hypoglycemic drugs partly control blood glucose levels[8,9]. Insulin therapy negatively affects a patient's daily life without preventing diabetes progress; therefore, novel strategies, including glycemic control or β-cell replacement, are essential[10,11].

Long-term use of drugs reducing blood glucose is associated with a lack of satisfactory treatment and low life expectancy in patients with type 2 diabetes. The costs of care and treatment of diabetes mellitus and its complications are so expensive[11]. Recently, the numbers of antihyperglycemic drugs for type 2 diabetes have increased. Prevalent antidiabetic medications, such as α-glucosidase inhibitors, thiazolidinediones and insulin, usually show some side-effects, among which weight gain and gastrointestinal distress are more common[12,13]. Islet transplantation is an efficient substitute for patients suffering from islet cell dysfunction and inpatients who fail ideal blood glucose control, despite using high doses of insulin[14-17]. Evidence shows that mesenchymal stem cells (MSCs) can be used in pancreatic islet cell therapy in diabetes patients[18-21]. Using molecular receptors and inhibitors (dipeptidyl peptidase-4

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inhibitors and glucagon-like peptide-1) have been considered as new efficient and safe therapies. However, at present, cell therapy is the most helpful treatment for diabetes mellitus[22,23].

Stem cells have potency for self-restoration and differentiation to various cells. These features have led to them being involved in curing various diseases. The role of MSCs in regenerative medicine has been well defined[24,25]. These cells are separated from diverse tissues, such as umbilical cords, dental pulp, bone marrow and adipose tissue[26,27]. According to animal studies and clinical trials, MSCs transplantation has a useful role in the treatment of various diseases, such as spinal cord injury, brain injury, liver disease, diabetes mellitus and refractory systemic lupus erythematous[28,29]. Another key aspect is that during intravenous injection, MSCs find their pathway to injured tissue[28].

In vitro and *in vivo* studies have shown the effects of MSCs on controlling glucose levels, which could be generalized to clinical cases[30]. As a result of multiple differentiation abilities of MSCs, they are considered as one of the targets of diabetes treatment. Therefore, MSCs have been suggested as a new cure goal for controlling insulin resistance, normalizing glycosylated hemoglobin amounts (HbA1c) and reducing insulin requirement[31-33]. We carried out this review to affirm the efficacy of mesenchymal stem cells on blood glucose, levels of HbA1c, C-peptide and insulin requirement.

METHODS

Search strategy

All searches were carried out in PubMed, Scopus, Web of Science and Central databases up to June 2018 using the following keywords: diabetes mellitus, mesenchymal stem cell and other related keywords based on MeSH entry terms. We also manually scanned references to select additional studies. Similar and duplicate articles were removed through EndNote software version X7 (Thomson Reuters, Philadelphia, PA, USA).

Inclusion and elimination criteria

Studies meeting the following criteria were selected: randomized controlled trials; studies in type 2 diabetes patients; and studies that assessed and compared the amounts of insulin requirement and blood glucose levels before and after mesenchymal stem cells therapy. Biomarkers that were investigated in each selected article included C-peptide levels, levels of HbA1c and insulin dose changes after mesenchymal cell therapy.

Data extraction

Two researchers reviewed full texts of the selected studies and evaluated their qualities. Differences between studies were defined through conversation. Then, data were sorted according to first author name, the year of publication, sample size, duration of study and the outcomes.

Quality assessment

The Jadad Score Scale was adjusted to evaluate the quality of the final studies selected. This scale independently recognizes the methodological quality of a clinical trial advising the effectiveness of blinding. The quality scores range from 0 to 5. If a study was low quality, it received a score of <3, and if a study was high-quality, a score of ≥3 was assigned.

Statistical analysis

Data were analyzed in Stata version 11 (StataCorp, College Station, TX, USA). Examination of heterogeneity was carried out in current meta-analysis to show variation in results. I^2 index was used to measure heterogeneity, and a value >50% was considered as heterogeneity. Also, the random effects model was used for pooled estimation. The factor clarifies the percentage of variation through studies, which showed the impression ratio of heterogeneity compared with chance on variation. Furthermore, forest plots were drawn for standardized mean differences (SMD) of outcomes.

RESULTS

Result of surveys and description of studies

According to the procedures selected, nine eligible clinical trials regarding the efficacy of mesenchymal stem cell therapy for type 2 diabetes with a collection of 57 articles were involved in the present analysis. Figure 1 shows all trials selected. The data from these articles are listed in Table 1. The mean age of patients was 52.32 years. In all studies, the therapeutic role of stem cells was evaluated in patients with type 2 diabetes. Classification of studies was carried out based on the source of stem cells; two studies used Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs; 83 patients), one study used MSCs and mononuclear cells (30 patients), one study used amniotic stem cells (54 patients), bone marrow mononuclear cells were used in two studies (152 patients), one study exerted human placenta-derived stem cells (PD-MSCs; 10 patients), one study injected umbilical cord mesenchymal stem cells to three patients and one study used umbilical cord mesenchymal stem cells (UCMSCs) (six patients). In two studies, control groups were only treated by insulin. In one study, there were three groups, including a control group, and in two studies, two types of stem cells (MSCs and mononuclear cells) were injected. In another six studies, patients were examined before and after stem cell transplantation.

MSCs therapy in type 2 diabetes patients

The influence of mesenchymal stem cell therapy on type 2 diabetes in nine trails among 227 patients, including 40 controls, is shown in Figure 1. The articles were reviewed and selected in three stages: reading, screening and eligibility.

Therapeutic effects of MSCs on levels of C-peptide

Three studies of all reviewed articles evaluated the therapeutic effects of mesenchymal stem cells on C-peptide levels. The cells used in these studies were human PD-MSCs, WJ-MSCs and amniotic stem cells. We observed no considerable heterogeneity between these studies (I^2 = 54.9%, P = 0.109), so the SMDs

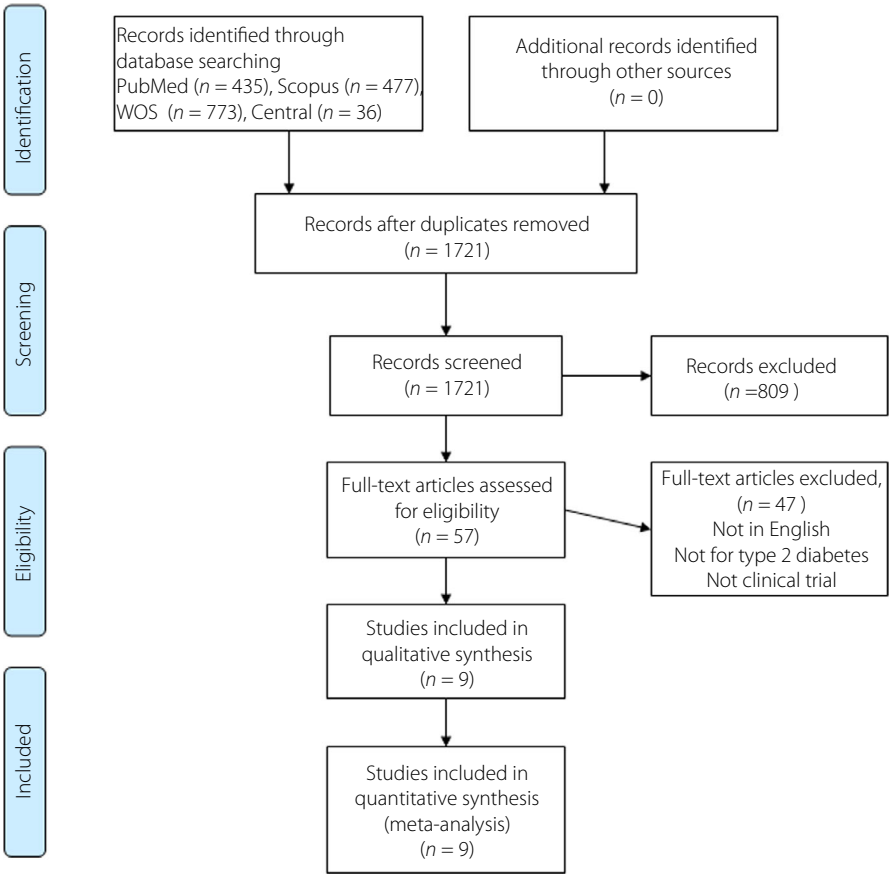

Figure 1 | Overview of study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

were merged and calculated by a fixed-effects model. According to the findings, treatment with MSCs compared with insulin therapy alone, did not have a remarkable effect on the C-peptide levels in type 2 diabetes patients (SMD 0.20, 95% CI −0.61 to 1.00; Figure 2). These outcomes prove that the C-peptide levels of patients who suffer from type 2 diabetes are not be affected by MSC treatment.

MSCs influence HbA1c levels

Seven studies surveyed the therapeutic effect or MSC on HbA1c levels, in which WJ-MSCs, PD-MSCs, amniotic fluid stem cells, mononuclear stem cells from bone marrow (BMMSCs) and umbilical cord mesenchymal stem cells (UCMSCs) were applied for cell therapy. There was a significant heterogeneity between these studies (I^2 = 88.6%, P = 0.000). The levels of HbA1c in patients with type 2 diabetes significantly reduced after mesenchymal stem cell therapy (SMD −1.45, 95% CI −2.10 to −0.79, Figure 3).

Mesenchymal stem cells decrease insulin dosage

The role of mesenchymal stem cells therapy on insulin dose in patients with type 2 diabetes in three studies was evaluated using WJ-MSCs, PD-MSCs and mononuclear stem cells from bone marrow (Figure 4). Based on I and P-values for the fixed-effects model, heterogeneity was observed between these studies (I^2 = 96.8%, P = 0.000). Stem cell therapy was found to significantly reduce insulin dosage in diabetes patients studied (SMD −1.40, 95% CI −2.88 to 0.09, Figure 4).

DISCUSSION

Some reasons, such as increasing consumption of glucose, genetic disorders, obesity and sedentary lifestyle, lead to a decrease in mass and function of pancreatic b-cells, and therefore a set of metabolic diseases is created, called diabetes mellitus[34,35]. Cellular therapies suggest a novel method in the treatment of type 2 diabetes. Former studies have shown that various stem cells, by differentiating into b-cells, which secrete insulin, improve treatment process and reduce blood glucose levels. However, there are short-term follow-up reports, and to carry out a profound study, long-term follow up is necessary[36].

In the current systematic review consisting of nine articles (from 2008 to 2013), we perused cell therapy, and its effect on levels of C-peptide, HbA1c and insulin dose in patients with type 2 diabetes. The combined results from three articles (2011,

Table 1 | Characteristics of studies included based on eligibility criteria

General Information			Methods		Participants						Outcome	
Author and year	Country	Jadad Score	Aims	Design	Control			case			Type of measure	Response rate
					Sample Size	Age_mean	Age_SD	Sample Size	Age_mean	Age_SD		
Shobhit; 2016	India	5	Effect of ABM-MSCs and ABM-MNCs transplantation in T2DM and prospect alterations in glucose level.	Clinical trial	10	53.5	–	20	47.5	–	C-peptide; HbA1c; insulin dose	–
Hu; 2016	China	4.5	Efficacy of infusion of WJ-MSCs in T2DM patient.	Hospital based: clinical trial	30	53.2		31	52.34		C-peptide; HbA1c; insulin dose	-
Liu; 2016	China	0	Clinical effects of amniotic cells transplantation in 4 patients with T2DM.	Hospital-based: case–control	–	–		4	54		C-peptide; HbA1c; insulin dose	-
Hu; 2012	China	4.5	Long-term effects of autologous bone marrow cells in the treatment of T2DM.	Hospital-based: clinical trials	56	50.4	4.9	62	50.2	8.2	C-peptide; HbA1c; insulin dose	-
Liu; 2014	China	2	Efficacy of WJ-MSC transplantation in T2DM patient by non-placebo phase I/II study.	Hospital based: clinical trial	-	-		22	59.2		C-peptide; HbA1c; insulin dose	-
Jiang; 2011	China	2	Therapeutic effect of PD-MSCs in T2DM with long-time dysfunction of islet cell, high insulin doses, also glycemic control.	Pilot clinical study: hospital	–	–		10	30–85		C-peptide; HbA1c; insulin dose	-
Tong; 2013	Michigan, USA	2.5	Efficacy of UCB transplantation in patients with T2DM.	Clinical Trial	–	–		3	Not reported		C-peptide; HbA1c; insulin dose	-
Guan; 2015	China	2	Effect of UCMSCs transplantation in T2DM patients.	Hospital: c linical trial	–	–		6	40.5	3.76	C-peptide; HbA1c; insulin dose	-
Fadini; 2015	Italy	2	Effects of statin discontinuation on EPCs, inflammation and *in vivo* angiogenesis.	Hospital: clinical trial	–	–		34	35–80		C-peptide; HbA1c; insulin dose	-

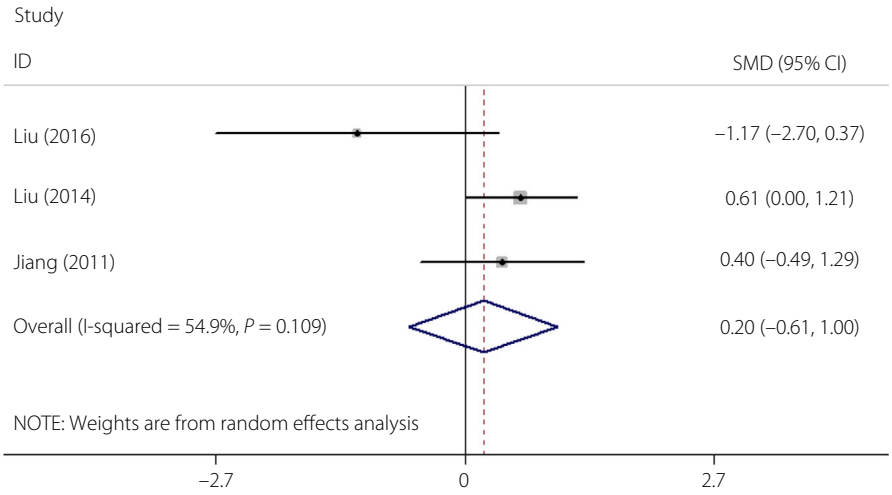

Figure 2 | Forest plot of C-peptide level in type 2 diabetes patients before and after mesenchymal cell therapy. CI, confidence interval; SMB, standardized mean differences.

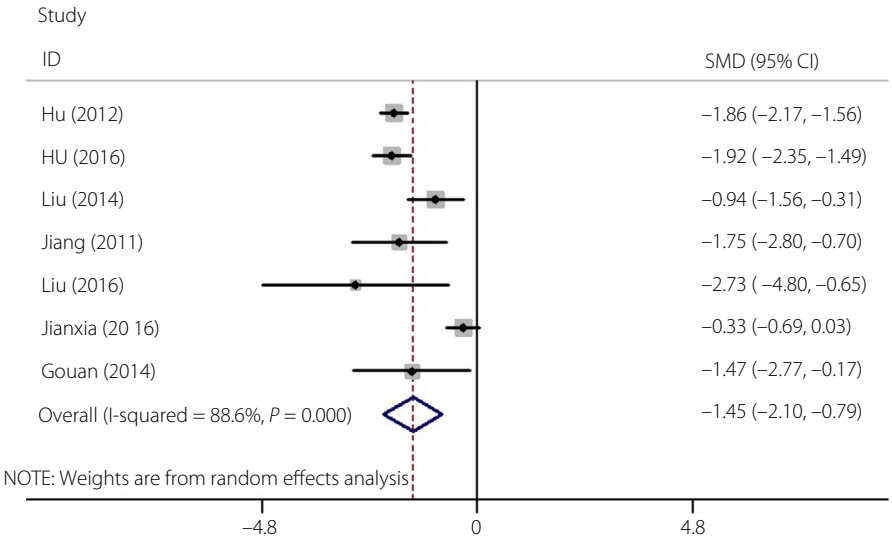

Figure 3 | Forest plot of glycosylated hemoglobin levels in patients with type 2 diabetes before and after mesenchymal cell therapy. CI, confidence interval; SMB, standardized mean differences.

2014 and 2016) showed that MSC therapy did not change C-peptide levels. In other words, MSCs did not induce C-peptide synthesis in β-cells of the pancreas, and the levels of precursor of insulin in patients with cell therapy were similar to those of the control group.

The HbA1c level investigations (from 2011 to 2016) showed reduced levels of HbA1c after stem cell therapy compared with non-stem cell-based therapy. HbA1c is a useful indicator of long-term blood glucose control, and based on these conclusions, cell therapy could successfully reduce blood glucose levels.

In the current systematic analysis, we also reviewed the effect of cell therapy on insulin dosage requirements, before and after treatment. The findings showed a significant role of stem cell therapy in reducing the daily insulin dose.

So far, many studies have examined the effects of stem cell transplantation therapy on various aspects of both type 1 and type 2 diabetes. Compared with different types of stem cell transplantation, mesenchymal stem cell transplantation in patients with diabetes has shown better therapeutic success[23,28,37-39], and is the main treatment in type 2 diabetes

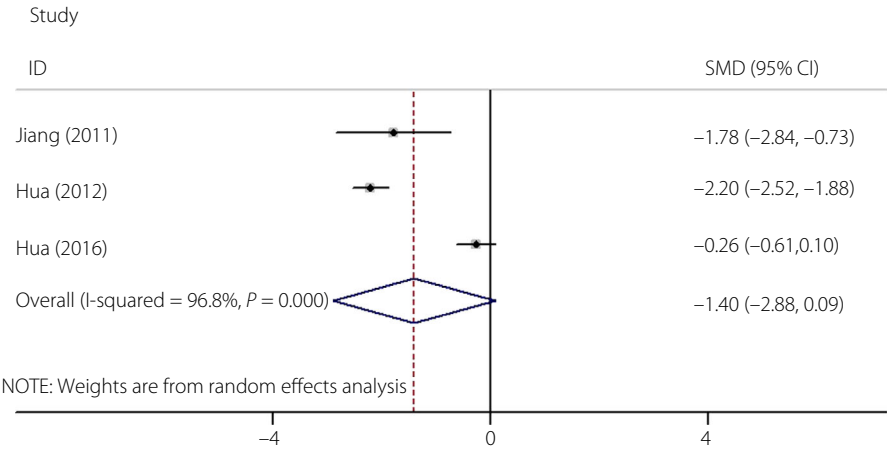

Figure 4 | Forest plot of insulin dose in patients with type 2 diabetes before and after mesenchymal cell therapy. CI, confidence interval; SMB, standardized mean differences.

associated with a decrease in insulin resistance[40]. In a review study by Rahim *et al.*, the mesenchymal cell transplantation was found to reduce the required daily insulin dose and HbA1c levels in the intervention group. In contrast, negative effects on the amount of C-peptide were observed[41].

Other studies on the effect of stem cell and bone marrow stem cell transplantation in the treatment of type 2 diabetes have yielded similar results to the current study (reduced HbA1c levels and daily insulin doses, and increased levels of C-peptide), despite using different sources of stem cells, (bone marrow and peripheral blood)[42,43].

Similar to the present results, Cho *et al.*[3] reported that MSCs therapy moderates the treatment process of diabetes patients, by reducing the daily insulin requirements and HbA1c levels, but they explained that C-peptide levels rise after stem cell therapies. The effects of MSCs on a patient's body were seen to be maintained for 2–4 weeks, even after serial injections[3]. Furthermore, in another review article, MSCs were found to improve diabetes mellitus after 3–43 months through decreasing insulin requirements and HbA1c levels, and also by increasing plasma levels of C-peptide[44]. Comparing these studies with our meta-analysis shows that analyzing the effectiveness of stem cells on C-peptide levels by meta-analysis methods, is so different from other review studies alone, and is a controversial subject for future studies.

In the present systematic review and meta-analysis, improved treatment of type 2 diabetes patients with MSCs was caused by reducing the levels of insulin dose and HbA1c levels. Further studies are required to clarify whether stem cells affect C-peptide gene expression or not. Also, more precise clinical assays on gene expression of upstream and downstream factors of C-peptide should be carried out.

There were some limitations to the present meta-analysis, which if they were removed, we would have better results and we could survey in a broad way. Some data were presented in the form of figures without any charts or any graphs, so data analyses and interpretation were difficult. Also, there were incompatible time limitations of some articles. These limitations led to lack of significance.

Based on present review and other studies, cell therapy is not a cure, but is a clinically safe method for ameliorating diabetes mellitus. Broad investigations to study the precise effect of cell therapy on diabetes patients, with more experimental details of humoral factors, cellular and molecular analysis, could be of great benefit in better conceiving this method in the treatment of diabetes, especially type 2 diabetes.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Luo JZ, Xiong F, Al-Homsi AS, *et al*. Allogeneic bone marrow co-cultured with human islets significantly improves islet survival and function in vivo. *Transplantation* 2013; 95: 801–809.
2. Le PT-B, Phu-Van Doan N, Van Tien P, *et al*. A type 2 diabetes mellitus patient was successfully treated by autologous bone marrow-derived stem cell transplantation: a case report. *Biomed Res Ther* 2019; 6: 2966–2969.
3. Cho J, D'Antuono M, Glicksman M, *et al*. A review of clinical trials: mesenchymal stem cell transplant therapy in type 1 and type 2 diabetes mellitus. *Am J Stem Cells* 2018; 7: 82.
4. Hu J, Wang Y, Gong H, *et al*. Long term effect and safety of Wharton's jelly-derived mesenchymal stem cells on type 2 diabetes. *Exp Therapeut Med* 2016; 12: 1857–1866.
5. Kahn S. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 2003; 46: 3–19.

6. Zaccardi F, Webb DR, Yates T, *et al*. Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. *Postgrad Med J* 2016; 92: 63–69.
7. Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. *Lancet* 2011; 378: 169–181.
8. Fukuhara T, Hyogo H, Ochi H, *et al*. Efficacy and safety of sitagliptin for the treatment of nonalcoholic fatty liver disease with type 2 diabetes mellitus. *Hepatogastroenterology* 2014; 61: 323–328.
9. Lechner A, Habener JF. Stem/progenitor cells derived from adult tissues: potential for the treatment of diabetes mellitus. *Am J Physiol Endocrinol Metab* 2003; 284: E259–E266.
10. Hinnen DA. Therapeutic options for the management of postprandial glucose in patients with type 2 diabetes on basal insulin. *Clin Diab* 2015; 33: 175–180.
11. Taylor R. Calorie restriction for long-term remission of type 2 diabetes. *Clin Med* 2019; 19: 37–42.
12. Prentki M, Nolan CJ. Islet β cell failure in type 2 diabetes. *J Clin Investig* 2006; 116: 1802–1812.
13. Sun Y-n, Zhou Y, Chen X, *et al*. The efficacy of dapagliflozin combined with hypoglycaemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomised controlled trials. *BMJ Open* 2014; 4: e004619.
14. Ciceri F, Piemonti L. Bone marrow and pancreatic islets: an old story with new perspectives. *Cell Transplant* 2010; 19: 1511–1522.
15. Kodama S, Kühtreiber W, Fujimura S, *et al*. Islet regeneration during the reversal of autoimmune diabetes in NOD mice. *Science* 2003; 302: 1223–1227.
16. Porat S, Weinberg-Corem N, Tornovsky-Babaey S, *et al*. Control of pancreatic β cell regeneration by glucose metabolism. *Cell Metab* 2011; 13: 440–449.
17. El Ouaamari A, Kawamori D, Dirice E, *et al*. Liver-derived systemic factors drive β cell hyperplasia in insulin-resistant states. *Cell Rep* 2013; 3: 401–410.
18. Ranjbaran H, Abediankenari S, Mohammadi M, *et al*. Wharton's jelly derived-mesenchymal stem cells: isolation and characterization. *Acta Medica Iranica*. 2018; 56: 28–33.
19. Ranjbaran H, Abediankenari S, Khalilian A, *et al*. Differentiation of Wharton's jelly derived mesenchymal stem cells into insulin producing cells. *Int J Hematol Oncol Stem Cell Res* 2018; 12: 220.
20. Ranjbaran H, Abediankenari S, Amiri MM. Enhanced differentiation of Wharton's jelly-derived mesenchymal stem cells in insulin-producing cells by the extract of nigella Sativa seeds. *Iran Red Crescent Med J* 2018; 20: e62111.
21. Ranjbaran H, Abediankenari S, Azadbakht M, *et al*. Differentiation of mesenchymal stem cells to insulin producing cells using the extracts of *Allium ursinum* and *Silybum marianum*. *J Mazandaran Univ Med Sci* 2017; 27: 1–12 (Persian).
22. Richter B, Bandeira-Echtler E, Bergerhoff K, *et al*. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. *Coch Database Syst Rev* 2008; 2: CD006739.
23. Vanikar A, Dave S, Thakkar U, *et al*. Cotransplantation of adipose tissue-derived insulin-secreting mesenchymal stem cells and hematopoietic stem cells: a novel therapy for insulin-dependent diabetes mellitus. *Stem Cells Int* 2010; 2010: 1–5.
24. Ling W, Zhang J, Yuan Z, *et al*. Mesenchymal stem cells use IDO to regulate immunity in tumor microenvironment. *Can Res* 2014; 74: 1576–1587.
25. Gharibi T, Ahmadi M, Seyfizadeh N, *et al*. Immunomodulatory characteristics of mesenchymal stem cells and their role in the treatment of multiple sclerosis. *Cell Immunol* 2015; 293: 113–121.
26. Li C-y, Wu X-y, Tong J-b, *et al*. Comparative analysis of human mesenchymal stem cells from bone marrow and adipose tissue under xeno-free conditions for cell therapy. *Stem Cell Res Ther* 2015; 6: 55.
27. Al-Nbaheen M, Ali D, Bouslimi A, *et al*. Human stromal (mesenchymal) stem cells from bone marrow, adipose tissue and skin exhibit differences in molecular phenotype and differentiation potential. *Stem Cell Rev Rep* 2013; 9: 32–43.
28. Jiang R, Han Z, Zhuo G, *et al*. Transplantation of placenta-derived mesenchymal stem cells in type 2 diabetes: a pilot study. *Front Med* 2011; 5: 94–100.
29. Pileggi A. Mesenchymal stem cells for the treatment of diabetes. *Diabetes* 2012; 61: 1355–1356.
30. Guan LX, Guan H, Li HB, *et al*. Therapeutic efficacy of umbilical cord-derived mesenchymal stem cells in patients with type 2 diabetes. *Exp Therap Med* 2015; 9: 1623–1630.
31. Coppell KJ, Kataoka M, Williams SM, *et al*. Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment—Lifestyle Over and Above Drugs in Diabetes (LOADD) study: randomised controlled trial. *BMJ* 2010; 341: c3337.
32. Lu Y, Wang Z, Zhu M. Human bone marrow mesenchymal stem cells transfected with human insulin genes can secrete insulin stably. *Ann Clin Lab Sci* 2006; 36: 127–136.
33. Dave S. Mesenchymal stem cells derived in vitro transdifferentiated insulin-producing cells: a new approach to treat type 1 diabetes. *Adv Biomed Res* 2014; 3: 266.
34. Liu Y, Guo L, Xu J. Amniotic stem cell transplantation therapy for type 2 diabetes: 3 years' follow-up report. *Eur Rev Med Pharmacol Sci* 2016; 20: 3877–3885.
35. Tuomilehto J, Lindström J, Eriksson JG, *et al*. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; 344: 1343–1350.
36. Lin Y, Sun Z. In vivo pancreatic β-cell–specific expression of antiaging gene klotho: a novel approach for preserving β-cells in type 2 diabetes. *Diabetes* 2015; 64: 1444–1458.
37. Carlsson P-O, Schwarcz E, Korsgren O, *et al*. Preserved β-cell function in type 1 diabetes by mesenchymal stromal cells. *Diabetes* 2015; 64: 587–592.

38. Hu J, Yu X, Wang Z, *et al*. Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus. *Endocr J* 2013; 60: 347–357.
39. Thakkar UG, Trivedi HL, Vanikar AV, *et al*. Insulin-secreting adipose-derived mesenchymal stromal cells with bone marrow–derived hematopoietic stem cells from autologous and allogenic sources for type 1 diabetes mellitus. *Cytotherapy* 2015; 17: 940–947.
40. Demchuk M, Ivankova O, Klunnyk M, *et al*. Efficacy of fetal stem cells use in complex treatment of patients with insulin-resistant type 2 diabetes mellitus. *J Stem Cell Res Ther* 2016. https://doi.org/10.4172/2157-7633.1000342
41. Rahim F, Arjmand B, Shirbandi K, *et al*. Stem cell therapy for patients with diabetes: a systematic review and meta-analysis of metabolomics-based risks and benefits. *Stem Cell Investig* 2018; 2: 40.
42. Guo X-J, Li F-J, He Y-Z, *et al*. Efficacy of autologous bone marrow mononuclear cell transplantation therapy for type 2 diabetes mellitus: an updated meta-analysis. *Diabetes Therapy* 2019; 10: 535–547.
43. Wang Z-X, Cao J-X, Li D, *et al*. Clinical efficacy of autologous stem cell transplantation for the treatment of patients with type 2 diabetes mellitus: a meta-analysis. *Cytotherapy* 2015; 17: 956–968.
44. Päth G, Perakakis N, Mantzoros CS, *et al*. Stem cells in the treatment of diabetes mellitus–focus on mesenchymal stem cells. *Metabolism* 2019; 90: 1–15.