

SUPPLEMENTARY DATA

The Clinical Efficacy and Safety of Stem Cell Therapy for Diabetes Mellitus: A Systematic Review and Meta-Analysis

Yazhen Zhang^{1,2}, Wenyi Chen^{1,2}, Bing Feng^{1,2}, Hongcui Cao^{1,2*}

¹State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

²Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou, China

SUPPLEMENTARY DATA

Supplementary Table 1. Search strategy.

Data source	Search terms
PubMed	#1 stem cells [Title/Abstract] #2 progenitor cells [Title/Abstract] #3 hematopoietic stem cells [Title/Abstract] #4 mesenchymal stem cells [Title/Abstract] #5 bone marrow mononuclear cells [Title/Abstract] #6 cell therapy [Title/Abstract] #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 #8 diabetes [Title/Abstract] #9 hyperglycemia [Title/Abstract] #10 #8 OR #9 #11 #7 AND #10 filters: clinical trial
Embase	#1 'stem cells': ti, ab #2 'progenitor cells': ti, ab #3 'hematopoietic stem cell': ti, ab #4 'mesenchymal stem cell': ti, ab #5 'bone marrow derived stem cell': ti, ab #6 'cell therapy': ti, ab #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 #8 'diabetes': ti, ab #9 'hyperglycemia': ti, ab #10 #8 OR #9 #11 #7 AND #10 #12 #11 AND ('clinical trial'/de OR 'clinical trial (topic)'/de) AND 'article'/it
The Cochrane Library	#1 (diabetes):ti, ab, kw OR (hyperglycemia):ti, ab, kw (Word variations have been searched) #2 (stem cells):ab OR (hematopoietic stem cells):ti, ab, kw OR (mesenchymal stem cells):ti, ab, kw OR (bone marrow mononuclear cells):ti, ab, kw AND (cell therapy):ti, ab, kw (Word variations have been searched) #3 #2 AND #1 in Trials
ClinicalTrials.gov	"diabetes" AND "stem cells" studies with Results

SUPPLEMENTARY DATA

Supplementary Table 2. Results of the Downs and Black methodological quality assessment.

Study	Items																											Total Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
Ye 2017	1	1	1	1	1	1	1	0	1	0	0	1	1	0	0	1	1	1	0 ^a	1	0 ^a	0 ^a	0	0	0 ^a	1	5	20
D'Addio 2014	1	1	1	1	1	1	0	1	1	0	0	1	1	0	0	1	1	1	0 ^a	0	0	1	0	0	0 ^a	1	5	20
Zhang 2012	1	1	1	1	0	1	1	0	1	1	0	1	1	0	0	1	1	1	0 ^a	1	1	1	0	0	0 ^a	1	5	22
Li 2012	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	1	1	1	0 ^a	1	1	0	0	0	0 ^a	1	5	23
Gu 2012	1	1	1	1	1	1	1	1	1	0	0	1	1	0	0	1	1	1	0 ^a	1	0	0	0	0	0 ^a	1	5	21
Snarski 2010	1	1	1	1	0	1	1	1	1	0	0	1	1	0	0	1	1	1	0 ^a	1	0	1	0	0	0 ^a	1	4	20
Couri 2009	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0	1	0	1	0 ^a	1	1	0	0	0	0 ^a	0	5	20
Voltarelli 2007	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0	1	0	1	0 ^a	1	0	0	0	0	0 ^a	1	5	20
Carlsson 2014	1	1	1	1	1	1	1	1	0	0	0	1	1	0	0	1	1	1	0 ^a	1	1	0 ^a	1	0	0 ^a	1	5	22
Hu 2013	1	1	1	1	0	0	0	1	1	0	0	1	1	1	1	1	1	1	0 ^a	0	0 ^a	1	1	1	0 ^a	1	5	22
Bhansali 2017	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1	0 ^a	1	1	0 ^a	1	0 ^a	0 ^a	1	5	25
Hu 2016	1	1	1	1	1	1	0	1	1	0	0	1	1	0	0	1	1	1	0 ^a	0	1	1	1	0	0 ^a	1	5	22
Skyler 2015	1	1	1	1	1	0	0	1	0	0	0	1	1	1	0	1	1	1	0 ^a	0	1	0	1	0 ^a	0 ^a	1	5	20
Guan 2015	1	1	1	1	1	1	1	1	1	0	0	1	1	0	0	1	1	1	0 ^a	1	1	1	0	0	0 ^a	1	3	21
Liu 2014	1	1	1	1	1	0	1	1	1	0	0	1	1	0	0	1	1	1	0 ^a	0	0 ^a	1	0	0	0 ^a	1	5	20
Jiang 2011	1	1	1	1	1	1	1	1	1	0	0	1	1	0	0	1	1	1	0 ^a	1	1	1	0	0	0 ^a	1	5	23
Bhansali 2017	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	1	1	1	0 ^a	1	1	0 ^a	0	0	0 ^a	1	4	22
Wu 2014	1	1	1	1	1	1	1	1	1	0	0	1	1	0	0	1	1	1	0 ^a	1	0 ^a	0 ^a	1	0	0 ^a	1	5	22
Bhansali 2014	1	1	1	1	1	1	1	0	1	1	0	1	1	1	0	1	1	1	0 ^a	1	1	1	1	0 ^a	0 ^a	1	5	25
Hu 2012	1	1	1	1	1	0	1	1	1	1	0	1	1	0	0	1	1	1	0 ^a	1	1	1	0	0	0 ^a	1	5	23
Bhansali 2009	1	1	1	1	1	1	1	1	1	1	0	1	1	0	0	1	1	1	0 ^a	1	0 ^a	1	0	0	0 ^a	1	5	23

Abbreviations: Items 1–10: Reporting; Items 11–13: External validity; Items 14–20: Internal validity – bias; Items 21–26: Internal validity - confounding (selection bias); Items 27: Power.

0^a: Item was unable to be determined, scored 0

SUPPLEMENTARY DATA

Supplementary Table 3A. Results of sensitivity analysis of C-peptide levels in patients with T1DM after BM-HSC therapy.

Study	MD 95% CI	p-value	tau ²	I ²
All studies included (random effects model)	0.49 (0.24, 0.74)	<0.001	0.06	93%
Omitting D'Addio 2014	0.38 (0.21, 0.54)	0.16	0.01	42%
Omitting Snarski 2010	0.47 (0.20, 0.74)	<0.001	0.07	95%
Omitting Voltarelli 2007	0.46 (0.17, 0.75)	<0.001	0.07	95%
Omitting Ye 2017	0.53 (0.25, 0.81)	<0.001	0.06	94%
Omitting Zhang 2012	0.56 (0.36, 0.76)	0.04	0.02	64%

Supplementary Table 3B. Results of sensitivity analysis of HbA1c levels in patients with T1DM after BM-HSC therapy.

Study	MD 95% CI	p-value	tau ²	I ²
All studies included (random effects model)	-4.11 (-5.11, -3.11)	<0.001	0.79	88%
Omitting Couri 2009	4.54 (-5.38, -3.70)	0.10	0.32	56%
Omitting D'Addio 2014	-4.32 (-6.22, -2.41)	<0.001	2.38	88%
Omitting Snarski 2010	-3.79 (-4.84, -2.74)	<0.001	0.73	90%
Omitting Ye 2017	-3.98 (-5.25, -2.70)	<0.001	1.01	91%

Supplementary Table 4A. Results of sensitivity analysis of C-peptide levels in patients with T2DM after MSC therapy.

Study	MD 95% CI	p-value	tau ²	I ²
All studies included (random effects model)	0.24 (-0.27, 0.76)	0.08	0.11	60%
Omitting Bhansali 2017	0.59 (0.06, 1.13)	0.58	0.00	0%
Omitting Jiang 2011	0.22 (-0.32, 0.76)	0.04	0.12	76%
Omitting Liu 2014	0.00 (-0.06, 0.07)	0.37	0.00	0%

SUPPLEMENTARY DATA

Supplementary Table 4B. Results of sensitivity analysis of C-peptide levels in patient T2DM after BM-MNC therapy.

Study	MD 95% CI	p-value	tau ²	I ²
All studies included (random effects model)	0.36 (0.08, 0.64)	<0.001	0.07	81%
Omitting Bhansali 2009	0.34 (-0.06, 0.73)	0.001	0.12	81%
Omitting Bhansali 2014	0.29 (0.02, 0.56)	<0.001	0.06	82%
Omitting Bhansali 2017	0.47 (0.28, 0.66)	0.12	0.02	49%
Omitting Bhansali 2017	0.41 (0.07, 0.74)	<0.001	0.08	84%
Omitting Wu 2014	0.34 (-0.05, 0.73)	<0.001	0.12	85%

Supplementary Table 4C. Results of sensitivity analysis of HbA1c levels in patients with T2DM after MSC therapy.

Study	MD 95% CI	p-value	tau ²	I ²
All studies included (random effects model)	-1.54 (-2.48, -0.61)	<0.001	0.72	85%
Omitting Bhansali 2017	-1.89 (-2.70, -1.08)	0.06	0.31	64%
Omitting Hu 2016	-1.37 (-2.49, -0.25)	0.005	0.75	81%
Omitting Jiang 2011	-1.23 (-2.17, -0.29)	<0.001	0.60	87%
Omitting Liu 2014	-1.72 (-3.03, -0.40)	<0.001	1.13	90%

Supplementary Table 4D. Results of sensitivity analysis of HbA1c levels in patients with T2DM after BM-MNC therapy.

Study	MD 95% CI	p-value	tau ²	I ²
All studies included (random effects model)	-0.51 (-1.13, 0.11)	<0.001	0.53	90%
Omitting Bhansali 2009	-0.39 (-1.12, 0.33)	<0.001	0.62	92%
Omitting Bhansali 2014	-0.65 (-1.28, -0.02)	<0.001	0.44	88%
Omitting Bhansali 2017	-0.67 (-1.28, -0.06)	<0.001	0.41	88%
Omitting Bhansali 2017	-0.60 (-1.28, 0.08)	<0.001	0.54	91%
Omitting Hu 2012	-0.34 (-0.97, 0.29)	<0.001	0.43	84%
Omitting Wu 2014	-0.38 (-1.14, 0.37)	<0.001	0.66	92%

SUPPLEMENTARY DATA

Supplementary Table 4E. Results of sensitivity analysis of FPG levels in patients with T2DM after MSC therapy.

Study	MD 95% CI	p-value	tau ²	I ²
All studies included (random effects model)	-0.49 (-2.60, 1.63)	<0.001	3.29	96%
Omitting Bhansali 2017	-1.29 (-2.92, 0.33)	0.03	1.10	79%
Omitting Hu 2016	0.44 (-0.74, 1.62)	0.08	0.52	67%
Omitting Liu 2014	-0.55 (-3.41, 2.31)	<0.001	4.18	98%

Supplementary Table 4F. Results of sensitivity analysis of FPG levels in patients with T2DM after BM-MNC therapy

Study	MD 95% CI	p-value	tau ²	I ²
All studies included (random effects model)	-0.53 (-1.53, 0.46)	<0.001	1.42	94%
Omitting Bhansali 2009	-0.38 (-1.49, 0.73)	<0.001	1.51	95%
Omitting Bhansali 2014	-0.75 (-1.87, 0.36)	<0.001	1.47	94%
Omitting Bhansali 2017	-0.80 (-1.87, 0.26)	<0.001	1.34	93%
Omitting Bhansali 2017	-0.69 (-1.89, 0.51)	<0.001	1.72	94%
Omitting Hu 2012	-0.25 (-1.13, 0.62)	<0.001	0.84	87%
Omitting Wu 2014	-0.31 (-1.41, 0.80)	<0.001	1.48	94%