Mesenchymal Stromal/Stem Cell-Based Therapies for Diabetes Mellitus: A Comprehensive Systematic Review and Meta-Analysis

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Supplementary Table 1 Queries used in PubMed, Scopus, and Web of Science databases

No.	Queries
#1	"Stem Cell, Mesenchymal" OR "Mesenchymal Stem Cell" or "Stem Cells, Mesenchymal" or "Bone Marrow Mesenchymal Stem Cells" OR "Bone Marrow Mesenchymal Stem Cell" OR "Bone Marrow Stromal Cells" OR "Bone Marrow Stromal Cell" OR "Bone Marrow Stromal Cells, Multipotent" OR "Multipotent Bone Marrow Stromal Cell" OR "Multipotent Bone Marrow Stromal Cells" OR "Adipose-Derived Mesenchymal Stem Cells" OR "Adipose Derived Mesenchymal Stem Cells" OR "Adipose-Derived Mesenchymal Stromal Cells" OR "Adipose Derived Mesenchymal Stromal Cells" OR "Mesenchymal Stem Cells, Adipose-Derived" OR "Mesenchymal Stem Cells, Adipose Derived" OR "Adipose-Derived Mesenchymal Stem Cell" OR "Adipose Derived Mesenchymal Stem Cell" OR "Adipose Tissue-Derived Mesenchymal Stem Cell" OR "Adipose Tissue Derived Mesenchymal Stem Cell" OR "Adipose Tissue-Derived Mesenchymal Stem Cells" OR "Adipose Tissue Derived Mesenchymal Stem Cells" OR "Adipose Tissue-Derived Mesenchymal Stromal Cells" OR "Adipose Tissue Derived Mesenchymal Stromal Cells" OR "Adipose Tissue-Derived Mesenchymal Stromal Cell" OR "Adipose Tissue Derived Mesenchymal Stromal Cell" OR "Mesenchymal Stromal Cells" OR "Mesenchymal Stromal Cell" OR "Stromal Cell, Mesenchymal" OR "Stromal Cells, Mesenchymal" OR "Multipotent Mesenchymal Stromal Cells" OR "Multipotent Mesenchymal Stromal Cell" OR "Mesenchymal Stromal Cells, Multipotent" OR "Mesenchymal Progenitor Cell" OR "Mesenchymal Progenitor Cells" OR "Progenitor Cell, Mesenchymal" OR "Progenitor Cells, Mesenchymal" OR "Wharton Jelly Cells" OR "Wharton's Jelly Cells" OR "Wharton's Jelly Cell" OR "Whartons Jelly Cells" OR "Bone Marrow Stromal Stem Cells"
#2	"Diabetes Mellitus, Noninsulin-Dependent" OR "Ketosis-Resistant Diabetes Mellitus" OR "Diabetes Mellitus, Non Insulin Dependent" OR "Diabetes Mellitus, Non-Insulin-Dependent" OR "Non-Insulin-Dependent Diabetes Mellitus" OR "Diabetes Mellitus, Stable" OR "Stable Diabetes Mellitus" OR "Diabetes Mellitus, Type II" OR "NIDDM" OR "Diabetes Mellitus, Noninsulin Dependent"

	OR “Diabetes Mellitus, Maturity-Onset” OR “Diabetes Mellitus, Maturity Onset” OR “Maturity-Onset Diabetes Mellitus” OR “Maturity Onset Diabetes Mellitus” OR “MODY” OR “Diabetes Mellitus, Slow-Onset” OR “Diabetes Mellitus, Slow Onset” OR “Type 2 Diabetes Mellitus” OR “Noninsulin-Dependent Diabetes Mellitus” OR “Noninsulin Dependent Diabetes Mellitus” OR “Maturity-Onset Diabetes” OR “Diabetes, Maturity-Onset” OR “Maturity Onset Diabetes” OR “Type 2 Diabetes” OR “Diabetes, Type 2” OR “Diabetes Mellitus, Adult-Onset” OR “Adult-Onset Diabetes Mellitus” OR “Diabetes Mellitus, Adult Onset”
#3	“Clinical Study” OR “Clinical Trial” OR “Clinical Trial, Phase I” OR “Clinical Trial, Phase II” OR “Clinical Trial, Phase III” OR “Clinical Trial, Phase IV” OR “Controlled Clinical Trial” OR “Randomized Controlled Trial”
#4	#1 (tiab) and #2 (tiab) and #3 (tiab)

Supplementary Table 2 Study the characteristics of articles that analyze the effects of mesenchymal stromal/stem cell (MSC)-based therapies for diabetes mellitus

Ref.	Type of study	Study design	Mesenchymal stem cell-based therapies					Outcomes
			Setting	Components	Period	Number of sessions	Session duration	
Vanikar et al. [1]	Clinical trial	Prospective, Longitudinal, Nonrandomized, open-label trial	Hospital-based laboratory for cell preparation; transplantation under general anesthesia	IS-AD-MSCs and CBM cells	The study was conducted from October 2007 to September 2008. Follow-up: mean 23 months.	Single transplantation session	Cell infusion completed at 6–8 mL/min over omental vein cannulation	Reduction in insulin dependency, improvement in HbA1c, increase in C-peptide levels, and reduction in DKA episodes.

Hu et al. [2]	Clinical Trial	Prospective, Longitudinal Randomized, controlled trial (double-blind)	The Stem Cell Center, Affiliated Hospital of the Medical College, Qingdao University	WJ-MSCs	Follow-up over 24 months	Single intervention	NA	The therapy demonstrated a significant improvement in glycemic control and β-cell function over the 24-month follow-up period compared to insulin therapy alone. Patients in

								the intervention group also had reduced insulin requirements, with some achieving insulin independence.
Hu et al. [3]	Phase I/II randomized controlled trial	Prospective, Longitudinal, Randomized, double-blind,	Infusion performed at the Stem Cell Center of the Affiliated Hospital of	WJ-MSCs	Two infusions over four weeks	Two	NA	Improved glycemic control, β-cell function, reduced diabetic

		controlled trial	Qingdao University.					complications, and decreased requirement for insulin and oral hypoglycemic drugs
Cai et al. [4]	Open-label Clinical Trial	Prospective, Longitudinal, Randomized, Parallel-arm Study	Conducted at a tertiary hospital in China.	UC-MSCs	12 months follow-up after treatment	Two infusions one month apart	30 minutes per session	Improved β-cell function in the intervention group was maintained over 12 months

								Reducing in the level of HbA1C, FBG, and Insulin requirements
Leão et al. [5]	Cohort study	Retrospective, Longitudinal, Non-Randomized, Open-Label Cohort Study.	University Hospital (Federal University of Rio de Janeiro - UFRJ)	Single infusion of ASCs	36 months	Single-dose ASC infusion	15-20 minutes for the infusion	All patients in the intervention group achieved partial CR at 6 months.
				Vitamin D supplementation (2000 IU				At 36 months, the intervention

			cholecalciferol daily for 12 months)			n group required 49% less total daily insulin compared to the control group, with similar glycemic control.
De Guzman et al. [6]	Case Series	Prospective, Longitudinal, Nonrandomized, Open-Label Case Series	Lung Center of the Philippines, Quezon City, Philippines	Autologous bone marrow-derived MSCs and EPCs	6 months	6 (one infusion per month)	NA	Reduction in the level of HbA1c, FPG, Creatinine, and BUN in patients

Moon et al. [7]	Clinical Trial	Prospective, Longitudinal, Randomized, Single-Blind, Parallel-Group, Comparator-Control Study	Four medical centers in South Korea.	ALLO-ASC-Sheet	12 weeks of treatment and evaluation	Weekly applications for up to 12 weeks	NA	Accelerating wound healing process, Faster and more significant size reduction in the treatment group, Post-hoc analysis indicated better outcomes for Wagner grade II ulcers

Nguyen et al. [8]	Open-label Clinical Trial	Prospective, Longitudinal, Randomized, Parallel-Arm Study	Vinmec Times City International Hospital, Hanoi, Vietnam.	Autologous BM-MSCs	Follow-up of 12 months after stem cell administration	Two infusions	30 minutes per infusion	Reduction in HbA1C Change in fasting blood glucose Increase in C-peptide levels Reduction in insulin requirements
Liu et al. [9]	Phase I/II clinical trial	Prospective, Longitudinal, Non-randomized,	General Hospital of Chinese People's	WJ-MSCs	1 Year	2 sessions	NA	The study demonstrated that WJ-MSC

non-placebo-controlled study	Armed Police Forces	transplantation is a promising therapeutic option for T2DM, providing long-term glycemic control, reducing insulin dependency, and improving systemic inflammatory and immunolo

								gical profiles.
Guan et al. [10]	Phase I, open-label, single-arm clinical trial	Prospective, Longitudinal, Non-randomized study	Hospital (Weifang People's Hospital)	Intravenous infusion of UCMSCs	24-44 months follow-up	2 sessions	15 minutes per session	Significant reduction in insulin requirements; three patients became insulin-independent. Significant improvement in fasting C-peptide, Cmax, and AUC.

								HbA1C levels reduced significantly and remained stable for 24 months. Fasting plasma glucose and postprandial glucose stabilized.
Packham et al. [11]	Phase I/II, placebo-controlled, dose-d,	Prospective, Longitudinal, Randomized,	Intravenous infusion of rexlemestr	Allogeneic bone marrow-derived mesenchym	60-week study, with primary outcomes measured	Single infusion	45 minutes	Improvement in renal function (eGFR and

escalation clinical trial.	Multicenter, double-blind, sequential dose-escalation study.	ocel-L (MPC)	al precursor cells (rexlemestrocel-L)	at 12 weeks post-infusion	mGFR) at 12 weeks. Reduction in inflammation (e.g., IL-6 levels). Safety profile assessed through adverse events, immune response, and renal function parameters.

Carlsson et al. [12]	Clinical Trial	Prospective, Longitudinal, Randomized, Open-label, Parallel-group, Pilot Study.	Uppsala University Hospital, Sweden.	Autologous MSCs derived from bone marrow	Single administration with follow-up over 1 year	One intravenous infusion	Approximately 20 minutes	Intervention group preserved or improved β-cell function (C-peptide levels) over 1 year
Purwati et al. [13]	Phase I clinical trial	Prospective, Longitudinal, Non-randomized interventional clinical trial	Administered via catheterization	Autologous adipose-derived MSCs	3 months	Single transplantation	NA	Significant reduction in both fasting and postprandial blood glucose levels. HbA1c values

improved over a 3-month period, showing better glycemic control. Increased C-peptide levels indicate improved pancreatic β-cell function. Reduction in insulin requirements

								suggests enhanced insulin sensitivity or endogenous insulin production.
Jiang et al. [14]	Open-label Pilot Study	Prospective, Longitudinal, Non-randomized, Parallel, Single-arm Clinical Trial	Liaoyang Diabetic Hospital, China	PD-MSCs	3 months follow-up after treatment	3 intravenous infusions (1-month intervals)	NA	Improved renal and cardiac function noted HbA1C reduced

								significantly Insulin requirement decreased significantly C-peptide levels increased
Bhansali et al. [15]	Placebo-controlled comparative study	Prospective, Longitudinal, Randomized, Parallel-group design	Clinical (hospital-based)	ABM-MSC and ABM-MNC	Single administration, with a 12-month follow-up	1 session per participant	NA	60% of participants in both the ABM-MSC and ABM-MNC groups achieved a

								≥50% reduction in insulin requirement while maintaining HbA1c <7.0%
Skyler et al. [16]	Phase II, placebo-controlled, dose-escalation clinical trial.	Prospective, Longitudinal, Randomized, Multicenter, single-blind study.	Single intravenous infusion of rexlemestrocel-L.	Allogeneic bone marrow-derived mesenchymal precursor cells (rexlemestrocel-L)	12-week primary study, with a 2-year safety follow-up.	One	45 minutes	HbA1c: Significant reduction in HbA1c in the 2.0 × 10^6/kg MPC group (-0.46%) compared to placebo at 8 weeks;

33% of participants in this group achieved HbA1c <7% versus 0% in placebo ($p < 0.05$).

Fasting Glucose: Small reductions in fasting plasma glucose in MPC groups compared

to placebo, not statistically significant. Inflammatory Markers: Reduced TNF-α and increased adiponectin in some MPC groups, indicating anti-inflammatory effects (non-

								significant overall).
Thakkar et al. [17]	Clinical trial	Prospective, Longitudinal, Non-randomized, open-labeled, two-armed clinical trial	Clinical, hospital-based procedure	Group 1: Autologous IS-AD-MSC and BM-HSC Group 2: Allogenic IS-AD-MSC and BM-HSC	Monitoring at 3-month intervals	Single co-infusion session	NA	Significant reduction in insulin requirement, Improved glycemic control (HbA1c), Increased serum C-peptide levels
Li et al. [18]`	Open-label, Single-arm Study	Prospective, Longitudinal, Non-randomized, parallel	Conducted at Shanghai Changhai Hospital,	Intravenous infusion of SHED	Treatment over 6 weeks with a 12-month follow-up	3 infusions over 42 days	15 minutes per infusion	Significant reduction in HbA1C and fasting blood

single-arm study.	Endocrinology Department	glucose during treatment. Insulin requirements reduced by 35.34% at the end of treatment and by 51.18% at 3 months post-treatment. Three patients became insulin-

								independent by the study's end
								Improvement in fasting C-peptide and 2-hour postprandial C-peptide levels
Lian et al. [19]	Clinical trial	Prospective, Longitudinal, Non-randomized, single-arm open-label study	Conducted at Peking University Shenzhen Hospital, Shenzhen, China.	hUC-MSCs	Weekly intravenous infusion for 3 weeks	Three infusions	Each infusion delivered over a single session	Improvement in glycemic control (HbA1c and fasting plasma glucose).

								Increased islet β-cell function (HOMA-β). Reduction in the dosage of hypoglycemic agents.
Zhao et al. [20]	Phase 1/2 Clinical Trial.	Prospective, Longitudinal, Randomized, Open-label, Parallel-group, Study.	Conducted at General Hospital of Jinan Military Command, Jinan, China.	CB-SCs are used in a device for immune modulation.	Single treatment with follow-ups at 4, 12, 24, and 40 weeks	One session	6–7 hours for lymphocyte isolation and exposure to CB-SCs in the device	Significant improvement in HbA1c and C-peptide levels, as well as a reduction in Insulin

								requirements
Wu et al. [21]	Open-label, controlled clinical trial.	Prospective, Longitudinal, Randomized study	Single-center (hospital-based, Fuzhou General Hospital).	Autologous BM-MNC infusion and HOT	12 months	20 sessions for HOT in BM-MNC+HOT group	1 hour per session	Improvements in glycemic control, islet function, and quality of life; reduction in HbA1c and insulin dependence.
Wu et al. [22]	Randomized Controlled Study	Prospective, Longitudinal, Randomized, Open-	900th Hospital of Joint Logistic Support	MSCs + MCs	8-year follow-up	Two infusions for Dual MSC + MC group,	Intra-arterial infusion lasting 15–20 minutes	Increase in C-peptide AUC in both Dual MSC + MC

label, Parallel-group Study	Force, Fujian Medical University, China	and MC-Only group, reduction in insulin requirement, and HbA1c and fasting blood glucose significantly improved at 1 year but gradually worsened over 8 years.

	MCs only	One infusion for MC-Only group	Reduction in diabetes-related complications

ABM-MNC, Autologous Bone Marrow-Derived Mononuclear Cells; ABM-MSC, Autologous Bone Marrow-Derived Mesenchymal Stem Cells; ALLO-ASC-Sheet, Allogeneic adipose-derived stem cell hydrogel sheets; ASC, Allogeneic adipose-derived stem cell; BM-HSC, Bone marrow-derived hematopoietic stem cells; BM-MNC, Bone marrow mononuclear cell; CBM, Cultured bone marrow; CB-SCs, Cord blood-derived multipotent stem cells; CR, clinical remission; DKA, Diabetic ketoacidosis; FBG, Fasting blood glucose; EPCs, endothelial progenitor cells; HbA1c, Glycosylated hemoglobin; HOT, hyperbaric oxygen therapy; hUC-MSCs, Human umbilical cord-mesenchymal stem cells; IDDM, Insulin-dependent diabetes mellitus; IS-AD-MSCs, Adipose tissue-derived insulin-secreting mesenchymal stem cells; MSCs, mesenchymal stem cells; PBG, Postprandial Blood Glucose; PD-MSCs, Placenta-derived mesenchymal stem cells; SHED, Stem cells from human exfoliated deciduous teeth; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; UCMSCs, Umbilical cord-derived mesenchymal stromal cells; WJ-MSCs, Wharton's Jelly Mesenchymal Stem Cells.

Supplementary Table 3 Participant characteristics of articles that analyzed the effects of MSC-based therapies for diabetes mellitus

Ref.	Year	Country	Characteristics of participants			Sample size (participants)		
			Condition	Sex	Age	Total	Intervention	Control
Vanikar et al. [1]	2010	India	IDDM	Mixed	Mean age 21.1 years (range: 13–43 years)	11	11	None
Hu et al. [2]	2013	China	Newly-onset T1DM	Mixed	Average 17.9 years	29	15	14
Hu et al. [3]	2016	China	Patients diagnosed with T2DM	Mixed	Mean age 52.7 ± 6.3 years	61	31	30
Cai et al. [4]	2022	China	T1DM with poor glycemic control despite insulin therapy.	Mixed	Mean age: 28 years	36	18	18
Leão et al. [5]	2024	Brazil	T1D patients diagnosed between 16-40 years old	Mixed	Intervention group (mean age at T1D	28	7	21

					onset): 27.28 ± 6.67 years Control group (mean age at T1D onset): 21 ± 5.32 years			
De Guzman et al. [6]	2024	Philippines	T2DM diagnosed for more than five years.	Mixed	53-68 years old	5	5	None
Moon et al. [7]	2019	South Korea	Patients with diabetic foot ulcers (Wagner grade I and II)	Mixed	Treatment Group: Mean age 59.9 ± 13.3 years. Control Group: Mean age 68.4 ± 9.9 years.	39	22	17
Nguyen et al. [8]	2021	Vietnam	T2DM patients with HbA1C	Mixed	Median age 59.5 years	30	30	None

			levels between 7.5% and 9.0% and fasting blood glucose <10 mmol/L.					
Liu et al. [9]	2014	China	T2DM with poor glycemic control	Mixed	Mean age 52.9 ± 10.5 years	22	22	None
Guan et al. [10]	2015	China	T2DM	Male	40.5 ± 3.76 years	6	6	None
Carlsson et al. [12]	2015	Sweden	Newly diagnosed T1DM with residual β-cell function.	Mixed	Intervention Group: Mean 24 ± 2 years. Control Group: Mean 27 ± 2 years.	20	10	10
Purwati et al. [13]	2017	Indonesia	T2DM	NA	30 - 79 years	40	40	None
Jiang et al. [14]	2011	China	T2DM patients with poor glycemic control	Mixed	45–82 years	10	10	None

			on high-dose insulin					
Bhansali et al. [15]	2016	India	T2DM with ≥5 years of disease duration, on triple oral anti-diabetic drugs and insulin therapy (≥0.4 IU/kg/day).	Mixed	30–60 years	30	10 in ABM-MSC group, 10 in ABM-MNC group.	10
Skyler et al. [16]	2015	United States.	T2DM with poor glycemic control on metformin alone or with one additional oral antidiabetic medication.	Mixed	57.2 years	61	0.3×10^6/kg MPC: 15 1.0×10^6/kg MPC: 15 2.0×10^6/kg MPC: 15	16

Thakkar et al. [17]	2015	India	Type 1 diabetes mellitus with >12 months duration, presence of glutamic acid decarboxylase (GAD) antibodies, and low serum C-peptide levels	Mixed	Group 1: Mean 20.2 ± 6.9 years. Group 2: Mean 19.7 ± 9.96 years.	20	10	10
Li et al. [18]`	2021	Republic of China	T2DM patients poorly controlled on insulin therapy	Mixed	48–64 years	24	24	None
Lian et al. [19]	2022	China	T2DM with HbA1c levels between 7% and 9.5%.	Mixed	Mean age 52.5 ± 7.91 years	16	16	None
Zhao et al. [20]	2012	China	Patients with T1D, both moderate (some residual β-cell function) and	Mixed	Median 29 years (range: 15–41 years)	15	12 participants (6 moderate	3

			severe (no residual β-cell function).				T1D, 6 severe T1D)	
Wu et al. [21]	2014	China	T2DM	Mixed	40-65 years	80	60	20
Wu et al. [22]	2024	China	Patients with T2DM	Mixed	40–65 years	97 enrolled, 89 completed follow-up	Dual MSC + MC Group: 33 participants MC-Only Group: 32 participants	31

Supplementary Table 4 Comparative RCTs that were not entered into the meta-analysis and the reason for exclusion

Author	The reason for the exclusion	Ref.
Vanikar et al.	The study does not have a Control group.	[23]
Hu et al.	This study has not represented adequate data	[24]
Hu et al.	This study has not represented adequate data	[3]
Moon et al.	This study has not represented adequate data	[25]
Bhansali et al.	This study has not specified the SD	[15]

Supplementary Table 5 Detailed information about various outcomes of the surveys in which the effects of MSC-based therapies for diabetes mellitus

Ref.	Type of study	The status of the population	Mesenchymal stem cell-based therapies			Level of evidence
			Name of outcome	Intervention group	Control group	
Vanikar et al. [1]	Prospective nonrandomized open-label clinical trial.	Patients diagnosed with IDDM, with an average disease duration of 8.2 years. Participants required insulin therapy and exhibited low serum C-peptide levels (<0.5 ng/mL).	HbA1c	Baseline: 8.47% (range: 6.2–10.3%). Post-intervention: 7.39% (range: 5.72–8.98%).	NA	Level 4

C-peptide Levels	Baseline: 0.1 ng/mL (range: 0.02–0.3 ng/mL). Post-Intervention: Increased to 0.37 ng/mL (range: 0.1–1.8 ng/mL).
Insulin Requirements	Baseline: 1.14 units/kg/day (range: 0.42–2.4 units/kg/day). Post-Intervention: Decreased to 0.63 units/kg/day (range: 0.09–1 units/kg/day).

Hu et al. [2]	Clinical Trial (Randomized Controlled Trial)	Patients with newly-onset T1DM, aged ≤ 25 years, with a diabetic duration of less than 6 months and fasting C-peptide ≥ 0.3 ng/mL.	HbA1c	Baseline: 6.85 ± 0.74% Post-Intervention (6 months): 5.5 ± 0.67%	Baseline: 6.79 ± 0.81% Post-Intervention (6 months): Remained slightly reduced for 6 months, then fluctuated; specific post-intervention values not provided.	Level 2
			FBG	Baseline: 102.6 ± 30.8 mg/dL Post-Intervention: Intervention Group: Decreased	Baseline: 97.2 ± 29.6 mg/dL Post-Intervention: No significant changes	

	to within the normal range	
PBG	Baseline: NA Post-Intervention: Achieved better control with fewer fluctuations.	Baseline: NR Post-Intervention: Larger fluctuations and remained higher
C-peptide Levels	Baseline: 0.85 ± 0.47 ng/mL Post-Intervention: Progressive increase, peaking at 12 months; precise values for long-term not provided.	Baseline: 0.89 ± 0.39 ng/mL Post-Intervention: Gradual decline; precise values not provided

			Insulin Requirements	Baseline: NA Post-Intervention: Significant reduction; 3/15 patients discontinued insulin, 8 reduced by more than 50%.	Baseline: NA Post-Intervention: Gradual increase in dosage	
Hu et al. [3]	Prospective, randomized, double-blind, controlled trial.	Patients with T2DM aged 42–6, treated with baseline therapies including diet, exercise, oral hypoglycemic	HbA1c	Baseline: 7.67 ± 1.23% Post-Intervention (6 months): 5.69 ± 0.79%	Baseline: 7.54 ± 1.31% Post-Intervention (6 months): Marginally reduced but fluctuated (specific value	Level 2

agents, and insulin.				not explicitly provided).
		FBG	Baseline: 148.3 ± 27.8 mg/dL Post-Intervention (3 months): 112 ± 18.7 mg/dL	Baseline: 142.31 ± 25.88 mg/dL Post-Intervention: Remained stable initially but began to rise after 15 months.
		C-peptide Levels	Baseline: 1.75 ± 0.64 ng/mL Post-Intervention (3 months): Increased progressively and stabilized for 15 months (specific post-intervention mean values not	Baseline: 1.83 ± 0.59 ng/mL Post-Intervention: Gradually decreased over time.

				explicitly provided).		
			Insulin Requirements	Baseline: 45.92 ± 8.87 U/day Post-Intervention: Reduced progressively; 32.3% of patients became insulin-free.	Baseline: 43.09 ± 10.3 U/day Post-Intervention: Increased over time, with 47% of patients requiring >50% higher insulin doses.	
Nguyen et al. [8]	Randomized, Open-label Clinical Trial	Adults with T2DM, HbA1C between 7.5% and 9.0%, fasting blood glucose <10 mmol/L, median age 59.5	HbA1c	Baseline: 8.2% ± 0.8% 3 months: 7.6% ± 0.6% 12 months: Return to baseline levels or slightly higher,	NA	Level 2

years, and M:F ratio 21:9		depending on subgroup analysis.
	FBG	Baseline: 8.6 ± 2.3 mmol/L 3 months: Reduction maintained within normal levels. 12 months: Maintained baseline levels.
	C-peptide Levels	Baseline: 1.6 (median, interquartile range 0.97–2.21) ng/mL. 12 months: Decrease in the IV

					group but slight increase in the DPA group.		
				Insulin Requirements	Insulin dose reduced by 6 IU/day in patients relying only on insulin after 12 months		
Liu et al. [9]	Phase prospective clinical trial	I/II	Patients with T2DM with poor glycemic control despite anti-diabetic therapies.	HbA1c	Decreased significantly from 8.20% to 7.0% at 12 months.	NA	Level 2
				FBG	Reduced from 7.53 mmol/L to 7.18 mmol/L at 12 months		

			PBG	Decreased from 14.96 mmol/L to 12.25 mmol/L		
			C-peptide Levels	Increased from 1.29 ng/mL to 1.86 ng/mL at 12 months.		
			Insulin Requirements	Reduced significantly; 7 out of 17 insulin-dependent patients became insulin-free.		
De Guzman et al. [6]	Prospective, Longitudinal, Nonrandomized, Open-Label Case Series	Diagnosed with T2DM for at least five years, with stable and non-progressive diabetic complications.	HbA1c	Mean reduction: 0.74%	NA	LEVEL 4

			FBG	Mean reduction: 1.484 mmol/L		
Guan et al. [10]	Phase I, open-label, single-arm clinical trial.	Patients with T2DM, are poorly controlled on insulin therapy.	HbA1c	Baseline: 8.55 ± 0.59% Post-intervention: Significantly decreased at 3 months and remained stable for 24 months	NA	LEVEL 4
			FBG	Baseline: Not specified in the document. Post-intervention: Stabilized		
			PBG	Baseline: Not specified in the document. Post-intervention: Stabilized		

C-peptide Levels	Baseline: Fasting C-peptide: 1.03 ± 0.12 ng/ml; Peak C-peptide (Cmax): 3.65 ± 0.68 ng/ml Post-intervention: Significantly increased
Insulin Requirements	Baseline: 0.43 ± 0.09 IU/kg/day Post-intervention: Reduced significantly (0.33 ± 0.07 IU/kg/day at 1 month, further reductions leading to insulin

				independence in three patients)		
Moon et al. [7]	Randomized, Single-Blind, Comparator-Controlled Clinical Trial.	Patients with diabetic foot ulcers (Wagner grade I and II), aged between 18–80 years, with a history of ulcers for over 4 weeks and adequate blood flow around the ulcer. The wounds were not infected, and participants had Type I or II diabetes.	HbA1c	Baseline: 7.9 ± 1.6% Post-intervention: Post-intervention HbA1c values are not reported	Baseline: 8.1 ± 1.7% Post-intervention: Post-intervention HbA1c values are not reported	Level 2
			PBG	Baseline:	Baseline:	

					193.0 ± 96.5 mg/dL Post-intervention: Post-intervention HbA1c values are not reported	208.5 ± 94.8 mg/dL Post-intervention: Post-intervention HbA1c values are not reported	
Purwati et al. [13]	Phase I clinical trial.	Patients with T2DM experiencing tertiary treatment failure.	HbA1c		Decreased from 8.28% to 6.79%.	NA	Level 2
			FBG		Decreased from 148.78 mg/dl to 102.33 mg/dl.		
			PBG		Decreased from 252.78 mg/dl to 129.16 mg/dl.		

			C-peptide levels	Increased from 2.44 ng/ml to 2.98 ng/ml.		
			Insulin requirements	Decreased from 8.74 pg/l to 7.19 pg/l.		
Jiang et al. [14]	Non-Randomized, Open-label Pilot Study	Adults with T2DM, aged 45–82 years (Mean: 66 years), with poorly controlled glycemic levels on high-dose insulin therapy	HbA1c	Baseline: 9.8% ± 2.2 Post-intervention: 6.7% ± 1.2	NA	Level 4
			C-peptide levels	Baseline: Mean ± SD: 4.1 ± 3.7 ng/mL Post-intervention: Mean ± SD: 5.6 ± 3.8 ng/mL		

			Insulin requirements	Baseline: 63.7 ± 18.7 IU/day Post-intervention: 34.7 ± 13.4 IU/day		
Bhansali et al. [15]	Randomized, single-blinded, placebo-controlled, comparative study	Patients with T2DM, disease duration ≥5 years, aged 30–60 years, on triple oral anti-diabetic drugs and insulin therapy (≥0.4 IU/kg/day)	HbA1c	Intervention Group (ABM-MSC): Reduced from 6.9% (baseline) to 6.4% (post-intervention at 12 months). Intervention Group (ABM-MNC): Increased from 6.7% (baseline) to 7.0% (post-	No significant change.	Level 2

	intervention at 12 months).	
C-Peptide Levels	Intervention Group (ABM-MSC): Modest increase from 0.7 to 0.8 nmol/L. Intervention Group (ABM-MNC): Significant increase from 0.7 to 1.1 nmol/L.	No significant change
Insulin Requirements	Intervention Group (ABM-MSC): Reduced by 54% at 12 months. Intervention Group (ABM-	No significant reduction

				MNC): Reduced by 51% at 12 months.		
Li et al. [18]`	Non-Randomized, Open-label, Single-arm Clinical Trial.	Adults (aged 48–64 years) with T2DM poorly controlled on insulin therapy.	HbA1c	Baseline: 8.38 ± 0.74% Post-treatment: Significantly reduced during the treatment period and maintained for 3 months post-treatment.	NA	Level 4
			FBG	Baseline: 9.10 ± 2.68 mmol/L Post-treatment: Reduced significantly during the		

	treatment period but returned to baseline during follow-up.
Fasting C-peptide	Baseline: 1.44 ± 0.76 ng/mL Post-treatment: Elevated, but not statistically significant
Postprandial C-peptide	Baseline: 3.22 ± 1.58 ng/mL Post-treatment: Significantly increased at the end of the treatment period and remained elevated during follow-up.

			Insulin Requirements	Baseline: 0.43 ± 0.09 IU/kg/day Post-treatment: Decreased by 35.34% at the end of treatment, 51.18% at 3 months post-treatment, and stabilized thereafter.		
Lian et al. [19]	Prospective single-arm open-label clinical trial.	Patients with T2DM were on stable doses of hypoglycemic agents for at least two months prior to the study.	HbA1c	Decreased from 7.8% (baseline) to 7.15% at day 84 ($P < 0.01$)	NA	Level 4

FBG	Reduced significantly from 9.34 mmol/L to 6.52 mmol/L at day 14 ($P < 0.01$)
C-Peptide Levels	Fasting C-peptide increased from 741.56 ± 464.50 pmol/L (baseline) to 903.64 ± 500.50 pmol/L and Postprandial C-peptide increased from 1596.70 ± 989.65 pmol/L (baseline) to 1747.15 ± 985.12 pmol/L.

			HOMA-β	Increased from 29.90 (baseline) to 40.97 at day 28 ($P < 0.01$).

Supplementary Table 6 The studies that have undergone meta-analysis with a high risk of bias and the reason for this high risk of bias

Authors	The section with a high risk of bias	The reason for this high risk of bias	Ref.
Cai et al.	Blinding of Participants and Personnel (Performance Bias)	The study was open-label, and no blinding was applied	[4]
	Blinding of Outcome Assessment (Detection Bias)	The outcome assessors (e.g., for laboratory results like HbA1C, fasting glucose) were not explicitly reported as blinded.	
Carlsson et al.	Blinding of Participants and Personnel (Performance Bias)	The study was open-label, meaning no blinding was applied	[12]
	Blinding of Outcome Assessment (Detection Bias)	Outcome assessors were not blinded, increasing the likelihood of detection bias.	
Thakkar et al.	Blinding of participants and personnel (performance bias)	The study was open-label, with no blinding of participants or personnel.	[17]
Zhao et al.	Blinding of Participants and Personnel (Performance Bias)	The study was open-label, with no blinding of participants or personnel.	[20]
Wu et al.	Blinding of Participants and Personnel (Performance Bias)	The study was open-label, meaning neither participants nor personnel were blinded.	[21]

Wu et al.	Blinding of Participants and Personnel (Performance Bias)	The study is an open-label clinical trial, meaning neither participants nor personnel were blinded, increasing the risk of performance bias.	[22]

Supplementary Table 7 The Safety Profile of studies in which the effects of MSCs on diabetes have been examined

Authors	Safety profile of study	Ref.
Vanikar et al.	The authors specifically note that there were no untoward side effects related to the stem cell infusion or the administration of the conditioning regimen. Over the mean follow-up period of 7.3 months (range: 2.2 months to 1 year), all patients survived and showed improvement in their condition without any fatal outcomes.	[1]
Hu et al.	No fatal effects are mentioned in the study	[2]
Hu et al.	Safety profile confirmed with no adverse effects such as immune reactions, liver damage, or infections.	[3]
Nguyen et al.	No severe adverse events; minor events like hyperglycemia and hypoglycemia were managed.	[8]
Leão et al.	The adipose tissue-derived stromal/stem cell (ASC) infusion was associated with mild and transient adverse effects, including: transient headache, mild local infusion reactions, tachycardia, abdominal cramps, local thrombophlebitis, transient mild eye floaters, central retinal vein occlusion, recurrence of a benign ovarian teratoma No serious long-term adverse effects were reported No fatal effects or deaths were reported in the study	[5]
Liu et al.	Mild/moderate fever in 3 patients, resolved spontaneously. Nausea, vomiting, and headache in 1 patient, resolved within a week. One case of subcutaneous hematoma at the injection site, resolved within 7 days. No major complications or late-onset side effects reported during the study period.	[9]
Guan et al.	No adverse effects or complications were reported during the study. The therapy was well-tolerated, with no immunological reactions or tumor formation observed.	[10]

Cai et al.	No serious adverse effects reported; minor side effects resolved spontaneously.	[4]
De Guzman et al.	No adverse effects were observed in any of the five patients who received the MSC and EPC therapy.	[6]
	One patient died due to complications related to chronic kidney disease and T2DM.	
Moon et al.	Ulcer recurrence: 2 cases in the treatment group within 6 months, both resolved	[7]
	No serious adverse events related to ASC treatment	
Packham et al.	No acute or serious treatment-related adverse events were observed	[11]
	Common events (e.g., peripheral edema, urinary infections) were mild to moderate and distributed similarly across groups.	
	No immunogenic reactions or donor-specific anti-HLA antibodies were sustained	
Purwati et al.	No adverse effects or complications from MSC transplantation were reported, emphasizing the safety of the intervention in this small cohort.	[13]
Jiang et al.	No serious adverse effects observed; improved renal and cardiac function noted.	[14]
	No immune rejection or other safety concerns reported.	
Skyler et al.	No treatment-related serious adverse events; mild/moderate adverse events included respiratory issues and gastrointestinal symptoms.	[16]
Li et al.	No serious adverse effects; mild side effects like transient fever, fatigue, and rash resolved spontaneously.	[18]
	Stable safety profile, with no liver or kidney dysfunction observed.	
	The frequency of hypoglycemia episodes decreased during follow-up.	
Lian et al.	Four participants experienced transient fever, and one participant had asymptomatic nocturnal hypoglycemia	[19]

	No serious adverse effects were reported. No significant changes in liver or kidney function	
Zhao et al.	No adverse events related to the therapy were reported.	[20]
Wu et al.	Adverse events were mild (e.g., transient abdominal pain and minor hemorrhage).	[21]
	Minimal to no adverse effects in long-term follow-up.	
Wu et al.	Perioperative adverse events: Mild abdominal pain, minor bleeding at the puncture site, fever and chills, and no cases of acute pancreatitis. Short-term adverse events: two cases of transient neutropenia in the Dual MSC + MC group, Upper respiratory tract infections, and no severe hypoglycemia. Long-term adverse events: No significant increase in malignancy risk. One case of lung cancer in the MC-Only group, and one case of gastric cancer in the Control group. No malignancies in the Dual MSC + MC group. Severe adverse events: No severe long-term adverse events were reported. No significant differences in uncontrolled hypertension or hyperlipidemia between groups. Fatal events: No deaths were reported during the 8-year follow-up.	[22]

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