Evidence-based Guidelines for the use of Stem Cell Therapy

Endocrinological Conditions Supplement

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Department of Health Research
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CONTENTS

ABBREVIATIONS

ABM-MNCs	:	Autologous Bone Marrow-Derived Mononuclear Cells
ABM-MSCs	:	Autologous Bone Marrow-Derived Mesenchymal Stem Cells
ADA	:	American Diabetes Association
Allo MPCs	:	Allogeneic Mesenchymal Precursor Cells
Allo UC-MSCs	:	Allogeneic Umbilical Cord-derived Mesenchymal Stem Cells
AUC C	:	Area Under the Curve of C-peptide Measurements
BMI	:	Body Mass Index
BM-MNCs	:	Bone Marrow Mononuclear Cells
BM-MSCs	:	Bone marrow-derived Mesenchymal Stem/Stromal Cells
CBC	:	Complete Blood Count
CI	:	Confidence Interval
CKD-EPI	:	Chronic Kidney Disease Epidemiology Collaboration
CLI	:	Critical Limb Ischemia
CPGR	:	C-peptide/Glucose Ratio
DMSO	:	Dimethyl Sulfoxide
ECG	:	Electrocardiogram
FBG	:	Fasting Blood Glucose
FBS	:	Fasting Blood Sugar
GBD	:	Global Burden of Disease
G-CSF	:	Granulocyte Colony-Stimulating Factor
GDG	:	Guideline Development Group
eGFR	:	Estimated Glomerular Filtration Rate
GRADE	:	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	:	Glycated Haemoglobin
HBV	:	Hepatitis B Virus
HCV	:	Hepatitis C Virus
HIV	:	Human Immunodeficiency Virus
HLA	:	Human Leukocyte Antigen
HSCs	:	Hematopoietic Stem Cells
IA	:	Intra Articular
IU	:	International Unit
IV	:	Intra Venous
LI	:	Lability Index
MD	:	Mean Difference
MMTT	:	Mixed Meal Tolerance Test
MCID	:	Minimal Clinically Important Difference
MPCs	:	Mesenchymal Progenitor Cells
PBMNCs	:	Peripheral Blood Mononuclear Cells
PICO	:	Population, Intervention, Comparison and Outcome
PRISMA	:	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QoL	:	Quality of Life
RCTs	:	Randomized Controlled Trial
RoB 2	:	Risk of Bias 2

SAEs	:	Severe Adverse Events
SCT	:	Stem Cell Therapy
SD	:	Standard Deviation
T1DM	:	Type 1 Diabetes Mellitus
T2DM	:	Type 2 Diabetes Mellitus
UC-MSCs	:	Umbilical Cord Mesenchymal Stem Cells
WJ MSCs	:	Wharton's Jelly-Derived Mesenchymal Stem Cells

1. DIABETES MELLITUS

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i. Key Question in PICO format:

In patients with Diabetes Mellitus (Type 1 and Type 2), what is the efficacy and safety of stem cell therapy as compared to usual care?

Population: Patients with Diabetes Mellitus (Type 1 and Type 2)
Intervention: Any stem cell and product derived from stem cells or their derivatives
Comparator: Usual Care/ Conventional Care
Critical Outcomes:

Type 1 DM - Efficacy: Insulin independence, Hypoglycemic episodes, Quality of Life; Safety: Serious adverse events, mortality, tumor formation

Type 2 DM - Efficacy: HbA1c levels, Insulin requirement; Safety: Serious adverse events, mortality, tumor formation

ii. Search Strategy:

PubMed, Embase, Web of science and Cochrane databases were searched for peer-review articles. There were no restrictions on the publication date.

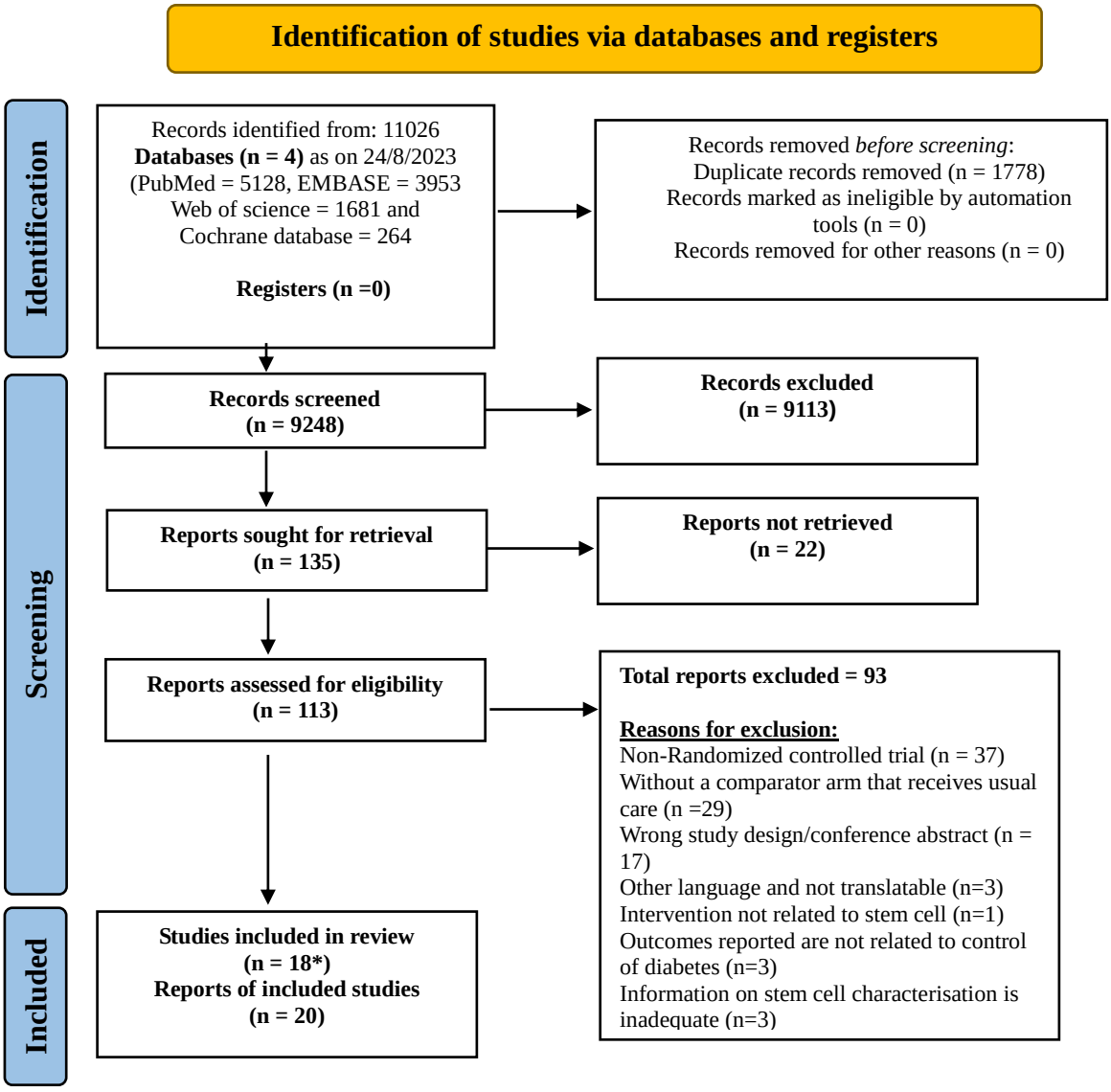
PubMed as on 29/8/2023		
Search domain	Search terms/strategy	No of hits
P	((diabetes) OR (diabetes mellitus) OR (IDDM) OR (hyperglycemia) OR (insulin resistance) OR ("insulin dependent"))	1038060
I	((stem cell*) OR (progenitor cell*) OR (hematopoietic stem cell*) OR (bone marrow mononuclear cell*) OR (mesenchymal cell*) OR (stromal cell*) OR (stem cell transplantation) OR (stem cell implantation) OR (bone marrow transplantation) OR (autologous) OR (allogenic) OR (stem cell graft))	902171
C	------Nil------- (Since standard of care or usual care as reported in studies will be considered, no specific search terms are applied for comparator group.)	-
O	------Nil------- (No specific search terms are considered for outcome, as it would be considered during screening of articles.)	-
S	(((randomized controlled trial) OR (randomised controlled trial) OR (controlled clinical trial) OR (clinical trial) OR (multicentric) OR (observational study) OR (follow up study) OR (trial[Title/Abstract]) OR (random* [Title/Abstract]) OR (control[Title/Abstract]) OR (placebo [Title/Abstract]) OR (follow-up[Title/Abstract]) OR (experimental[Title/Abstract]))) NOT ((animals[MeSH Terms]) NOT (humans[MeSH Terms]))	6261583
P&I&C&O&S	((diabetes) OR (diabetes mellitus) OR (IDDM) OR (hyperglycemia) OR (insulin resistance) OR ("insulin dependent")) AND ((stem cell*) OR (progenitor cell*) OR	**5128**

	(hematopoietic stem cell*) OR (bone marrow mononuclear cell*) OR (mesenchymal cell*) OR (stromal cell*) OR (stem cell transplantation) OR (stem cell implantation) OR (bone marrow transplantation) OR (autologous) OR (allogenic) OR (stem cell graft)) AND (((randomized controlled trial) OR (randomised controlled trial) OR (controlled clinical trial) OR (clinical trial) OR (multicentric) OR (observational study) OR (follow up study) OR (trial[Title/Abstract]) OR (random* [Title/Abstract]) OR (control[Title/Abstract]) OR (placebo [Title/Abstract]) OR (follow-up[Title/Abstract]) OR (experimental[Title/Abstract]))) NOT ((animals[MeSH Terms]) NOT (humans[MeSH Terms]))	
EMBASE on 29/8/2023		
Search domain	Search terms/strategy	No of hits
P	('diabetes mellitus'/exp OR 'diabetes' OR 'diabetes mellitus' OR 'diabetic' OR 'hyperglycemia'/exp OR 'glucose blood level, elevated' OR 'glycemia, hyper' OR 'hyperglucemia' OR 'hyperglycaemia' OR 'hyperglycemia' OR 'hyperglycemic syndrome' OR 'insulin resistance'/exp OR 'insulin resistance' OR 'resistance, insuline')	
I	('stem cell'/exp OR 'cell, stem' OR 'precursor cell' OR 'progenitor cell' OR 'stem cell' OR 'stem cells' OR 'hematopoietic stem cell'/exp OR 'bone marrow stem cell' OR 'haematopoietic precursor cell' OR 'haematopoietic progenitor cell' OR 'haematopoietic stem cell' OR 'haematopoietic stem cells' OR 'hematocytopoietic stem cell' OR 'hematopoietic precursor cell' OR 'hematopoietic progenitor cell' OR 'hematopoietic stem cell' OR 'hematopoietic stem cells' OR 'hemocytopoietic stem cell' OR 'hemopoietic stem cell' OR 'bone marrow derived mononuclear cell'/exp OR 'bone marrow derived mononuclear cell' OR 'bone marrow mononuclear cell' OR 'mesenchymal stem cell'/exp OR 'mesenchymal progenitor cell' OR 'mesenchymal stem cell' OR 'mesenchymal stem cells' OR 'stem cell, mesenchymal' OR 'stem cell transplantation'/exp OR 'stem cell based therapy' OR 'stem cell therapy' OR 'stem cell transplantation' OR 'transplantation, stem cell' OR 'bone marrow transplantation'/exp OR 'bone marrow cell transfer' OR 'bone marrow graft' OR 'bone marrow grafting' OR 'bone marrow transfusion' OR 'bone marrow transplant' OR 'bone marrow transplantation' OR 'transplantation, bone marrow' OR 'autologous stem cell transplantation'/exp OR 'autologous stem cell therapy' OR 'autologous stem cell transplantation' OR 'allogeneic stem cell transplantation'/exp OR 'allogeneic stem cell transplantation' OR 'allogenic stem cell transplantation'**)**	
C	------Nil------- (Since standard of care or usual care as reported in studies will be considered, no specific search terms are applied for comparator group.)	-
O	------Nil------- (No specific search terms are considered for outcome, as it would	-

	be considered during screening of articles.)	
S	('randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'follow up study' OR 'observational study' OR 'randomized controlled trial' OR 'trial, randomized controlled' OR 'clinical trial'/exp OR 'clinical drug trial' OR 'clinical trial' OR 'major clinical trial' OR 'trial, clinical')	
P&I&C&O&S	('diabetes mellitus'/exp OR 'diabetes' OR 'diabetes mellitus' OR 'diabetic' OR 'hyperglycemia'/exp OR 'glucose blood level, elevated' OR 'glycemia, hyper' OR 'hyperglucemia' OR 'hyperglycaemia' OR 'hyperglycemia' OR 'hyperglycemic syndrome' OR 'insulin resistance'/exp OR 'insulin resistance' OR 'resistance, insuline') AND ('stem cell'/exp OR 'cell, stem' OR 'precursor cell' OR 'progenitor cell' OR 'stem cell' OR 'stem cells' OR 'hematopoietic stem cell'/exp OR 'bone marrow stem cell' OR 'haematopoietic precursor cell' OR 'haematopoietic progenitor cell' OR 'haematopoietic stem cell' OR 'haematopoietic stem cells' OR 'hematocytopoietic stem cell' OR 'hematopoietic precursor cell' OR 'hematopoietic progenitor cell' OR 'hematopoietic stem cell' OR 'hematopoietic stem cells' OR 'hemocytopoietic stem cell' OR 'hemopoietic stem cell' OR 'bone marrow derived mononuclear cell'/exp OR 'bone marrow derived mononuclear cell' OR 'bone marrow mononuclear cell' OR 'mesenchymal stem cell'/exp OR 'mesenchymal progenitor cell' OR 'mesenchymal stem cell' OR 'mesenchymal stem cells' OR 'stem cell, mesenchymal' OR 'stem cell transplantation'/exp OR 'stem cell based therapy' OR 'stem cell therapy' OR 'stem cell transplantation' OR 'transplantation, stem cell' OR 'bone marrow transplantation'/exp OR 'bone marrow cell transfer' OR 'bone marrow graft' OR 'bone marrow grafting' OR 'bone marrow transfusion' OR 'bone marrow transplant' OR 'bone marrow transplantation' OR 'transplantation, bone marrow' OR 'autologous stem cell transplantation'/exp OR 'autologous stem cell therapy' OR 'autologous stem cell transplantation' OR 'allogeneic stem cell transplantation'/exp OR 'allogeneic stem cell transplantation' OR 'allogenic stem cell transplantation') AND ('randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'follow up study' OR 'observational study' OR 'randomized controlled trial' OR 'trial, randomized controlled' OR 'clinical trial'/exp OR 'clinical drug trial' OR 'clinical trial' OR 'major clinical trial' OR 'trial, clinical')	3953
Web of Science on 24/8/2023		
Search domain	Search terms/strategy	No of hits
P	ALL=(diabetes OR diabetes mellites OR hyperglycemia OR insulin dependent)	1137384
I	ALL=(stem cell OR stem cell transplantation OR stem cell therapy OR mesenchymal stem cells OR hemopoietic stem cell)	653839

C	------Nil------- (Since standard of care or usual care as reported in studies will be considered, no specific search terms are applied for comparator group.)	-
O	------Nil------- (No specific search terms are considered for outcome, as it would be considered during screening of articles.)	-
S	ALL=(randomized controlled study OR clinical trial OR observational study OR follow up study OR randomised trial OR randomised controlled trial)	2370101
P&I&C&O&S	(ALL=(diabetes OR diabetes mellites OR hyperglycemia OR insulin dependent)) **AND (**ALL=(stem cell OR stem cell transplantation OR stem cell therapy OR mesenchymal stem cells OR hemopoietic stem cell)) **AND (**ALL=(randomized controlled study OR clinical trial OR observational study OR follow up study OR randomised trial OR randomised controlled trial))	**1681**
Cochrane library		
Search domain	Search terms/strategy	No of hits
P	diabetes (in All Text)	118048
I	stem cell (in All Text)	16179
C	------Nil------- (Since standard of care or usual care as reported in studies will be considered, no specific search terms are applied for comparator group.)	-
O	------Nil------- (No specific search terms are considered for outcome, as it would be considered during screening of articles.)	-
S	trial (in All Text)	2043531
P&I&C&O&S	diabetes in All Text **AND** stem cell in All Text **AND** trial in All Text	454

iii. PRISMA flow diagram:



*Wu et al. 2022 is a follow-up study of Cai et al. 2016
Esfahani et al. 2015 is a follow-up study of Ghodsi et al. 2012

iv. Summary of included studies:

Study	Population	Intervention	Comparator	Outcomes
Perico et al. 2023[1]	Participants were between 40 and 85 years with type 2 DM for 3 or more years	Intravenous administration 12/4; Allo BM Mesenchymal stromal cell; 80 million cells	Placebo infusion	FBG, HbA1c, adverse events
Carlsson et al. 2023[2]	In one part, 9 male participants, 18-40 years of age with newly diagnosed type 1 diabetes were included. In second part there were 15 participants (10/5) and women were allowed to participate in part B	Intravenous administration 10/5; Allo WJ Mesenchymal stromal cell; 200 million cells	Placebo infusion	HbA1c, FBG, Insulin requirement, fasting c-peptide & MMTT, AUC c-peptide
Izadi et al. 2022[3]	A total of 21 patients (8 to 40 years) enrolled in this study. The patients were diagnosed with T1D according to diagnostic criteria and the ADA guidelines within six weeks before enrollment based on previous studies and were already under classic insulin therapy.	Intravenous administration 11/10; Auto BM MSCs; 1 million cells / kg	Placebo infusion	FBG, HbA1c, C-peptide, endogenous insulin, hypoglycemic episodes, adverse events and QoL
Ghodsi et al. 2012[4]	Thirty patients with type 1 diabetes and twenty-six with type 2 diabetes were selected according to the on following criteria: Age range between 10-60 years old, duration of the disease up to 20 years, blood glucose under 15mmol/l (270 mg/dl)	Intravenous administration 28/28; Allo HSCs; 35 million cells	Placebo solution	FBG, HbA1c, fasting C-peptide, insulin free period
Zang et al. 2022[5]	Patients aged between 20 and 65 years; diagnosed with T2DM for < 20 years (HbA1c levels between 7.0% and 12.0% and fasting C-pep tide levels of ≥ 1 ng/mL; and body mass index (BMI) of 24–40 kg/m^2	Intravenous administration 45/46; Allo UC MSCs; 1x10 million cells/kg	Placebo	FBG, reduction in insulin requirement, insulin free period, HbA1c, fasting C-peptide

Wu et al. 2022[6]	Patients of age 18-40 years, history of T1D 2 years and 16 years, hemoglobin A1c (HbA1c) 7.5% (58 mmol/mol) and 10.5% (91 mmol/mol), fasting serum C-peptide 14 of 21 patients in the SCT group and 15 of 21 patients in the control group completed follow up	IA 21/21; Allo UC stromal cell+ auto BMMNCs Mesenchymal UC-MSCs: 1.1 million cells/kg +Autologous BM-MNCs: 106.8 million cells/kg	Standard Care	FBG, incidence of end-organ dysfunction, HbA1c, fasting C-peptide, insulin dose requirement, hypoglycemic episodes and adverse events
Mirzaei et al. 2021[7]	20 diabetic patients aged 50-70 years with erectile dysfunction	Corpus cavernosum of penis 10/10; Auto MSCs 50-60 million cells	Normal Saline	FBG, HbA1c
Estrada et al. 2019[8]	A total of 23 (13/10) patients with T2DM (duration 5–15 years at baseline) were randomized	IA 13/10; Auto BM MNCs NM	Standard Treatment	FBG, C-peptide, insulin requirement, HbA1c
Sood et al. 2017[9]	A total of 21 patients comprising three groups of 7 patients each. Cells were infused into the superior pancreaticoduodenal artery (Group I), splenic artery (Group II) and through the peripheral intravenous route (Group III). Another group of 7 patients acted as controls and a sham procedure was carried out on them (Group IV).	IA and IV 21/7; Auto BM MNCs; 6.88 ± 2.30 x 10^8	Sham Procedure	Fasting C-peptide, reduction in insulin dose, HbA1c
Packham et al. 2016[10]	The study population was male and female patients ≥45 and ≤85 years old with type 2 diabetes and advanced diabetic nephropathy (e.g. eGFR 20–50 ml/min/1.73 m^2)	IV 20/20; Allo MPCs; 150 - 300 million cells	Placebo	HbA1c & adverse events
Hu et al. 2016[11]	A total of 61 patients with T2DM were randomly divided into two groups on the basis of basal therapy; patients in group I were administered WJ-MSC intravenous infusion twice, with a four-week interval, and patients in group II were treated with normal saline as control	IV 31/30; Allo WJ MSCs; 1 million cells /kg	Normal Saline	HbA1c, FBG, fasting C-peptide, insulin requirement, incidence of diabetic complications
Cai et al. 2016[12]	Forty-two patients (22 female and 20 male) were randomized into an SCT group (n = 21 receiving UC-MSCs + BM-MNCs trans plantation and standard clinical treatment) or a continued	IA 21/21; Allo UC Mesenchymal stromal cell + auto BM MNCs UC-MSC: 1.1 million cells kg	Standard Clinical Treatment	HbA1c, FBG, daily insulin requirements, C-peptide, AUC C-peptide, adverse events and QoL

	standard clinical treatment (control) group (n = 21)	+ autologous BM-MNC: 106.8 million cells /kg		
Nasli-Esfahani et al. 2015[13]	56 patients with type one (n=30) and type 2 (n=26) diabetes	IV 56/56; Allo HSCs; 35 - 55 million cells	Placebo	Incidence of retinopathy, neuropathy, ischemic heart disease, nephropathy and adverse events
Bhansali et al. 2014[14]	26 patients (13/13) with T2DM, age ranging from 30 to 70 years, having diabetes for ≥5 years with failure of triple oral antidiabetic drugs in optimal doses (metformin 2g per day, glimepiride 4mg per day, pioglitazone 15 mg per day) and requiring insulin (≥0.4 IU/kg per day) for at least 1 year to achieve optimal glycaemic control.	IA and IV 13/13; Auto BM MNCs; 3.2 (2.4 - 5.6) million cells	Placebo	HbA1c, insulin requirement, stimulated C-peptide
Haller et al. 2013[15]	15 eligible children with type 1 diabetes were randomized (10 treated and 5 control subjects)	10/5; UC blood NM	Intensive diabetes management	HbA1c, peak C-peptide, AUC C-peptide, insulin dose, safety
Hu et al. 2013[16]	Out of 29 patients with newly onset T1DM fifteen patients participated in the WJ-MSCs treatment group (group I), while the other 14 patients participated in control group (group II).	15/14; Allo WJ MSCs $2.6 \pm 1.2 \times 10^7$ ($1.5 - 3.2 \times 10^7$)	Normal Saline	FBG, HbA1c, C-peptide and C-peptide/glucose ratio. insulin free period, adverse events
Huang et al. 2005[17]	Twenty-eight diabetic patients with CLI were enrolled and randomized to either the transplant group or the control group.	14/14; Auto BM MNCs $3x10^9$	Intravenous injection of 90-200 μg/day prostaglandin E1	FBG
Bhansali et al. 2016[18]	30 patients were randomized into three groups in ratio 1:1:1 by random allocation software ABM-MSCs gp, ABM-MNCs gp and control	20/10 I:Auto BM MSCs II:BMMNCs 1×10^9/kg & 1×10^9	Sham Procedure	HbA1c, insulin requirement, fasting c-peptide & AUC C-peptide
Skyler et al. 2015[19]	Subjects (21 women, 40 men) with a mean ± SD baseline HbA1c 8.3 ± 1.0% (67± 10.9 mmol/mol), BMI 33.5 ± 5.5 kg/m^2, and diabetes duration 10.1 ± 6.0 years were enrolled at 18 U.S. sites.	45/16; Allo MPCs 0.3-2 million cells /kg	Placebo	HbA1c, hypoglycemic episodes, fasting plasma insulin, C-peptide

Carlsson et al. 2015[20]	Twenty-two patients newly diagnosed with type 1 diabetes	11/11; Auto BM Mesenchymal Stromal Cell 2.1–3.6 million cells	Insulin Treatment	HbA1c, insulin dose requirement, C-peptide

v. Classification of studies on the basis of level of manipulation of the stem cell/ Stem cell derived product used (*interpreted by the Secretariat as defined by CDSCO* and the information provided in the trial itself*):

DIABETES MELLITUS 1:

S.No.	Trial Details	Intervention	Level of manipulation	Comments
1.	Hu et al. 2013	WJ-MSCs	More	*"The WJ-MSCs were cultured and expanded in laminar flow laboratory for 4 passages to prepare final cell products"*
2.	Carlsson et al. 2023	WJ-MSCs	More	*"The investigational product ProTrans is a clinical-grade cell suspension of MSCs procured from donated Wharton's jelly tissue and expanded in adherent culture over approximately 4–5 weeks (a maximum of three passages) according to Good Manufacturing Practice (GMP)."*
3.	Wu et al. 2022	UC-MSCs	More	*"MSCs utilized in the trial were obtained from a single human donor umbilical cord. MSCs were cultured and expanded until passage four or five at the hospital cell center as per standard practice and in accordance with 2006 International Society for Cell & Gene Therapy criteria."*
4.	Cai et al. 2016	UC-MSCs	More	*"After reaching 80% confluence, UC-MSCs were harvested with 0.25% trypsin and 0.02% EDTA, replated at a density of 0.5–1 3 10^6 cells in a 175-cm2 flask, and incubated for 5–7 days. UC-MSCs were frozen at passage 2. Ten to 14 days before transplantation, cells were thawed and grown again until passage 4 or 5."*

5.	Izadi et al. 2022	BM-MSCs	More	*"Clinical-grade MSCs were isolated from bone marrow, expanded in passages 2–3, and cryopreserved under good manufacturing practice (GMP) conditions."*
6.	Carlsson et al. 2015	BM-MSCs	More	*"Clinical-grade MSCs were then generated under good manufacturing practice conditions as accredited by the Swedish National Board of Health and Welfare in growth media supplemented with lysed human platelets. All cells were harvested in pas sage 1–2 and cryopreserved before infusion."*
7.	Huang et al. 2005	Granulocyte colony–stimulating factor (G-CSF)–mobilized peripheral blood mononuclear cells (PBMNCs)	Less	*"300 ml suspension of blood circulating PBMNCs were collected from patients treated with G-CSF, through a Version 4 blood-cells separator (Cobe, Lakewood, CO) and concentrated."*
8.	Eshafani et al. 2015	Fetal liver-derived hematopoietic stem cells (HSCs)	Less	*"Total cell count in the prepared suspension was approximately 35-55 × 106, twenty percent of which was recognized as hematopoietic (CD34+) stem cells."*
9.	Haller et al. 2013	Umbilical Cord Blood Infusion	Less	*"Peripheral blood and an aliquot of UCB from potential subjects were shipped to the University of Florida for infectious disease testing, HLA confirmation, and vi ability screening. Thereafter, the UCB unit of qualified subjects was shipped to the University of Florida and stored until transfused."*
10.	Ghodsi et al. 2012	Fetal Liver-Derived Cell Suspension	Less	*"Total cell count in the prepared suspension was approximately 35-55×106, twenty percent of which was recognized as hematopoietic (CD34+) stem cells."*

DIABETES MELLITUS 2:

S.No.	Trial Details	Intervention	Level of manipulation	Comments
1.	Bhansali et al. 2014	BM-MNCs	Less	*"The mononuclear cells (MNCs) were separated by ultracentrifugation after layer ing on density-gradient medium (Ficoll-Hypaque, Sigma Aldrich, St. Louis, MO, USA) and were washed using phosphate-buffered saline (PBS; Himedia Laboratories Private Limited, Mumbai, India) and resuspended in nor mal saline with a final product volume of 8–10 ml."*
2.	Bhansali et al. 2016a	Bone marrow cells (cultured)	More	*"These cells were expanded up to 4-5 passages to obtain targeted cell numbers (1 million cells per Kg body weight) for infusion."*
3.	Bhansali et al. 2016b	Autologous bone marrow-MNCs	Less	*"The mononuclear cells (MNCs) were separated by centrifugation after layering on density gradient medium (Ficoll-Hypaque, Sigma- Aldrich, St. Louis, MO, USA), and were washed using phosphate-buffered saline (PBS; Himedia Laboratories Private Limited, Mumbai, India) and resuspended in normal saline with a final product volume of 8–10 ml."*
4.	Estrada et al. 2019	Autologous bone marrow stem cell transplantation	Less	*"Briefly, using centrifugation, gravity flow, and the various bags of the quadruple bag system, red cells were discarded in the second bag, the buffy coat was collected in the third bag, and the plasma and fat were discarded with the first bag. The buffy coat was washed and resuspended in isotonic normal saline in the third bag for the final product. The aspirate was a buffy coat pool containing EPCs and a few mesenchymal stem cells."*
5.	Ghodsi et al. 2012	Fetal Liver-Derived Cell Suspension	Less	*"Total cell count in the prepared suspension was approximately 35-55×106, twenty percent of which was recognized as hematopoietic (CD34+) stem cells."*

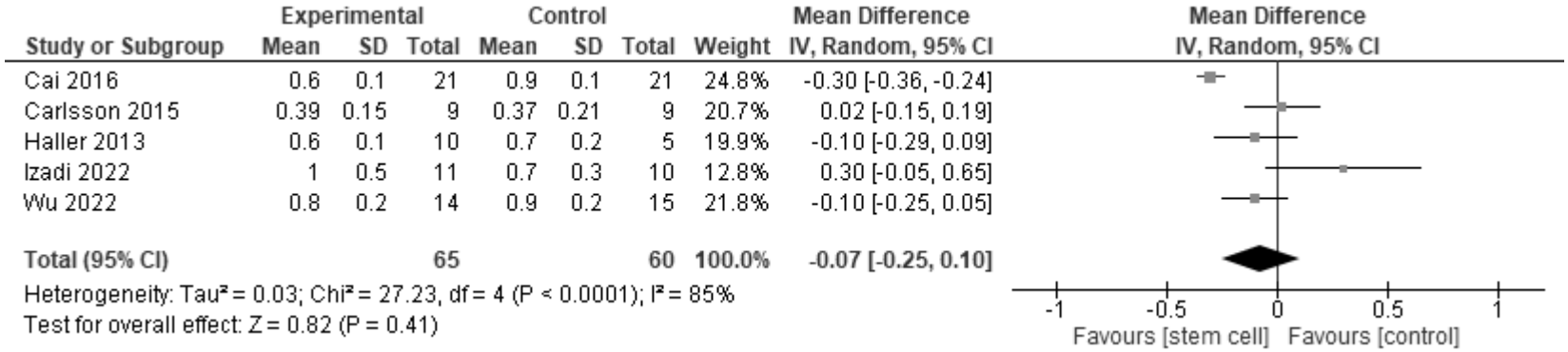
6.	Hu et al. 2016	WJ MSCs	More	*"WJ-MSCs were cultured and expanded in a laminar flow laboratory, which was designed according to good manufacturing practice conditions, for four passages to prepare the final cell products."*
7.	Perico et al. 2023	ORBCEL-M-Allogenic mesenchymal stromal cells	More	*"Cells were primarily expanded to passage 1."*
8.	Sood et al. 2017	BM-MNCs	Less	*"Bone marrow mononuclear cells were separated and purified using centrifugation."*
9.	Zang et al. 2022	UC-MSCs	More	*"Once cells reached sub confluence, tissue pieces were removed and cells adhering to the dishes were digested and passaged into flasks for further expansion."*
10.	Packham et al. 2016	Allogenic Mesenchymal precursor cell: rexlemestrocel-L	More	*"Immuno-selected, culture-expanded, immature subfraction of adult, bone marrow–derived mononuclear cells from healthy paid adult donors."*
11.	Skyler et al. 2015	Allogenic Mesenchymal precursor cell: rexlemestrocel-L	More	*"Immuno-selected, culture-expanded, immature subfraction of adult, bone marrow–derived mononuclear cells from healthy paid adult donors."*
12.	Esfahani et al. 2015	Fetal cell transplantation	Less	*"Total cell count in the prepared suspension was approximately 35-55 × 106, twenty percent of which was recognized as hematopoietic (CD34+) stem cells."*

* as defined by CDSCO in Annexure- I of the guideline document.

vi. Additional Forest plots:

1. Insulin Requirement in Type 1 Diabetes Mellitus: Evidence from 5 trials with a total of 125 participants reporting the insulin requirement yielded a mean difference of -0.07 (95% CI: -0.25 to 0.10) IU/day between the stem cell arm and the usual care arm. The difference was statistically non- significant.

1.1. Forest plot of Insulin requirement in Type 1 Diabetes Mellitus:



vii. Evidence to Decision Framework:

Should stem cell transplantation vs. usual care be used for Diabetes Mellitus (Type 1 and 2)?	
POPULATION:	Diabetes Mellitus (Type 1 and 2)
INTERVENTION:	Stem cell transplantation
COMPARISON:	Usual care
MAIN OUTCOMES:	**Type 1 DM** - Efficacy: Insulin independence, Hypoglycemic episodes, Quality of Life; Safety: Serious adverse events, mortality, tumor formation **Type 2 DM** - Efficacy: HbA1c levels, Insulin requirement; Safety: Serious adverse events, mortality, tumor formation
SETTING:	Hospital
PERSPECTIVE:	Health Systems/Population

BACKGROUND:	Diabetes is a serious, chronic disease characterized by elevated blood glucose levels caused by either insulin deficiency or insulin resistance. Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease characterized by destruction of insulin-producing beta cells in the pancreas leading to insulin deficiency while Type 2 Diabetes Mellitus is a chronic metabolic disorder characterized by insulin resistance. The chronic hyperglycemic state due to diabetes leads to complications such as retinopathy, neuropathy and nephropathy, if adequate glycemic control is not maintained. The standard of care for T1DM is frequent glucose monitoring and insulin replacement therapy through various insulin preparations. T2DM is predominantly treated with oral hypoglycemic drugs and may require insulin in later stages of the disease for optimum control. Diabetes management requires significant physical, mental and psychological effort from the patients and their families. Since diabetes is a chronic disease, there is an unmet need to search for curative therapeutic options to preserve or regenerate beta cells and maintain glucose homeostasis.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○No ○Probably no ○Probably yes ●Yes ○Varies ○Don't know	As per the GBD estimates in 2021, there were 529 million (95% uncertainty interval [UI] 500–564) people living with diabetes worldwide, and the global age-standardized total diabetes prevalence was 6.1% (5.8–6.5)[21].	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Type 1 DIABETES MELLITUS** **Insulin independence:** Three trials with 73 participants reported insulin independence at the end of one year post transplantation. The evidence showed a 5% absolute increase [RD: 0.05 (-0.08 to 0.19)] in insulin independence. However, the risk difference was statistically non-significant. **Hypoglycemic episodes:** Three studies with a total of 68 participants reported hypoglycemic episodes among type 1 Diabetes Mellitus patients. Out of these, data from two studies could be pooled for meta-analysis. The evidence suggested a 3% absolute increase [RD: 0.03, 95% CI (-0.14, 0.20)] in incidence of hypoglycemic episodes in stem cell arm as compared to usual care. However, the difference was statistically non-significant. Both the studies reporting hypoglycemic index used stem cells with more than minimal manipulation. Izaddi et al. 2022[4] reported hypoglycemic rates as events per patient-year. There were 24 events per patient-year in stem cell arm as compared to 34 events per patient-year in usual care arm at the end of one year. **Quality of life:** Evidence from 2 trials with a total of 63 participants reporting Quality of Life (QoL) at 12 months yielded a mean difference of 3.15 (95%CI: -0.80 to 7.10) between the stem cell arm and the usual care arm. The difference was statistically non-significant. Both the studies reporting quality of life used stem cells with more than minimal manipulation. **Type 2 DIABETES MELLITUS** **HbA1C**: Evidence from 8 trials with a total of 276 participants reporting HbA1c percentage at 6 months yielded a mean difference of -0.06 (95% CI: -0.63 to 0.52) between the stem cell arm and the usual care arm. Seven trials with 247 participants showed a mean difference of -0.10 (95% CI: -0.68 to 0.47) at the end of 12 months. The differences at both the time points were statistically non-significant. **Insulin Requirement:** Evidence from 6 trials with a total of 236 participants reporting the insulin requirement yielded a mean difference of -13.45 (95% CI: -21.75 to -5.14) IU/day at the end of six months between the stem cell arm and the usual care arm. Five trials with 207 participants showed a mean difference of -17.83 (95% CI: -26.45 to -9.21) IU/day at the end of twelve months. The differences at both the time points were statistically significant and more than MCID of 8 units, therefore, clinically important.	

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Type 1 DM**: Seven studies with a total of 169 participants reported serious adverse events in a follow-up ranging between 3-36 months. The evidence suggested a 1% absolute increase in the incidence of SAEs [RD: 0.01, 95% CI (-0.05, to 0.06)] in the stem cell arm as compared to usual care. There is no statistically significant difference in SAE between the two groups. The SAE reported by Carlsson et al. 2023[3] was unrelated to investigational product as participant became pregnant and was terminated from the trial. Nasli-Esfahani et al. 2015[14] reported a case of transitional meningioma causally related to stem cell transplantation. **Type 2 DM:** Six studies with 188 participants reported serious adverse events in a follow-up ranging between 3-36 months. There is no statistically significant difference in SAE [RD:0.00 95% CI (-0.06 to 0.06)] between the two groups. Perico et al. 2023[2] and Packham et al. 2016[11] with 46 participants have reported SAEs. Study by Packham et al. reported adverse events such as acute myocardial infarction, anemia, asthma, congestive heart failure, syncope and upper gastrointestinal hemorrhage in usual care arm and atrial fibrillation, renal failure chronic, benign prostatic hyperplasia, gangrene and diverticulitis, in stem cell arm. Perico et al. 2023[2] reported bronchospasm in usual care arm while acute myocardial infarction, congestive heart failure, COVID-19 positive, anemia with increased dyspnea, left hip fracture, respiratory tract infection, complicated duodenal diverticulitis, respiratory failure, hyperkalemia, multiple myeloma and headache in stem cell arm.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence in this review is of very low quality due to high risk of bias, inconsistency and imprecision in the effect shown by stem cell therapy.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Main outcome is clinical improvement in the form of decreased insulin dependence and which is likely to be highly valued by most patients.	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ●Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	It is less clear if benefits of stem cell intervention outweigh the harms, based on limited evidence.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
●Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of the resources required in stem cell transplantation was identified. However, indirect evidence shows that the average price of a Stem cell therapy for Diabetes type 1 in India is in the range of $5,500 USD to $8000 USD. The cost of treatment in other European countries costs approx. $25,000 - $30,000. But, in India, it will cost almost 70% to 80% less.[22]	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ○ Low ● Moderate ○ High ○ No included studies	No research evidence was identified.	The GDG members were fairly certain that stem cell therapy requires large resources.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ● Probably favors the comparison ○Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence was identified.	The intervention was not found to be effective and hence the committee deferred to comment on cost effectiveness.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	As stem cell therapy is an expensive treatment offered only at tertiary centres, it is likely to reduce equity.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Despite uncertainty regarding the medical risks and benefits associated with stem cell injections, patient may still consider undergoing treatment in private, unregulated clinics.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Feasible to implement in tertiary care centres.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Use only in the context of rigorously conducted randomized controlled trials**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○	○

CONCLUSIONS

Recommendation

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of Diabetes mellitus (type 1 and type 2). It may be used only in the context of rigorously conducted randomized controlled trials.

Justification

This recommendation has been made as there is very low certainty evidence of trivial improvement in glucose control and quality of life in patients with diabetes mellitus. In patients with Type 1 Diabetes Mellitus, there was trivial improvement in insulin independence and quality of life. In patients with Type 2 Diabetes Mellitus, there was a small reduction in the insulin requirement in the stem cell group as compared to usual care. However, the reduction in HbA1C was statistically non-significant between the two groups. Hence, the committee decided to make the overall judgement of desirable effects as trivial.

In both the groups, there is a small increase in undesirable effects with the use of stem cell therapy. Results should be interpreted with caution, in view of various study limitations like high risk of bias, small number of participants and/or events in the included studies and different sources of stem cell use. In addition, the follow up period was too small to comment on the side effect profile and long-term safety.

viii. Data Extraction Sheet:

Literature retrieved from database was imported into Rayyan software and duplicate records were removed. Two authors independently screened the title and abstracts and full-text articles using the predefined inclusion and exclusion criteria. The discrepancies in the selection of articles between the two authors were resolved by the third author. Two authors independently extracted the data using a piloted structured data extraction form in concurrence with the third reviewer. The characteristics of the 20 included studies are presented in the table below. The studies were published from 2005 to 2023 and were conducted in Argentina, Australia, China, Ireland, Italy, United Kingdom, Sweden, India, Iran, and the United States with sample sizes ranging from 15 to 91 patients. The studies included patients with T1DM (9 studies), T2DM (11 studies), one study included both type of diabetes and one study did not mention the type of diabetes. These patients had an average diabetes history ranging from recent onset to 19.6 years. The follow-up period ranged from 3 to 96 months. As per the design of these studies were considered, six were open label randomized controlled trials, six studies were single blinded, seven studies were double blinded and one study was triple blinded randomized controlled trial. Intervention reported in studies is as follows: 9 studies used mesenchymal stem cells, 5 studies used bone marrow mononuclear cells, 2 studies reported combination of mesenchymal stem cells and bone marrow mononuclear cells, 1 reported umbilical cord blood, 2 studies with each using hematopoietic stem cells and mesenchymal precursor cells, respectively. Eleven studies used saline as placebo in the control arm while other studies used usual diabetic care (4 studies), human serum albumin and DMSO (1 study), Cryostar CS10 fluid (1 study), prostaglandin E1 (1 study) and unspecified placebo/control in two studies.

Data extraction was done in Microsoft Excel sheet and analysed using 'Stata Statistical Software: Release 17 College Station, TX: StataCorp LP. Cochrane Risk of bias tool 2.0 was used to assess risk of bias of the randomized controlled studies included in systematic review for each of study outcomes (insulin requirement, C-peptide, fasting blood glucose, HbA1c, adverse events and hypoglycaemic episodes). Two reviewers independently assessed the risk of bias in studies and disagreements were resolved through discussion or by third reviewer. Risk of bias assessment for randomized controlled studies were conducted assessing sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Based on this as assessment, risk of bias in studies were rated as high, unclear and low.

Data synthesis:

Study characteristics of included studies for systematic review were tabulated following qualitative analysis. Meta-analysis for each outcome variable, comparing efficacy and safety of any stem cell vs. usual care was conducted when these data points were available from four or more studies. Standard methods suggested in Cochrane methods were used for data harmonisation before analysis. In trials reporting outcomes at baseline and endline of trial, effect estimate reported at end of trial was compared between intervention and control for meta-analysis.

Summary measures and handling heterogeneity of data:

Meta-analysis was carried separately for studies that included type 1 and 2 diabetes mellitus patients, as follows -

- For continuous variables, pooled mean difference (with 95% CI) of insulin requirement, and HbA1c between intervention and control group reported at end of study follow-up.
- Pooled incidence risk ratio with 95% confidence intervals for reporting adverse events and hypoglycaemic episodes between intervention and control group, was reported.

Sensitivity analysis was explored using "leave-one out" analysis technique to understand how each of the included studies influenced pooled estimate value. Statistical heterogeneity was assessed using Chi-square test ($P<0.05$) and I^2 statistic. Source of heterogeneity in studies was explored using subgroup analysis including place of study, type of stem cell administered and route of administration. If I^2 is greater than 50%, pooled analysis was based on random effects model DerSimonian and Laird approach. A fixed effects model using Mantel-Haensz el method was used if I^2 is less than 50%.

Meta-biases:

Meta-biases such as publication bias of included studies and selective outcome reporting bias was assessed. In case of having >10 studies included in meta-analysis, publication bias was assessed through visualization of funnel plot. Selective reporting bias of reported trials was assessed by comparing the list of outcomes reported in study results to the published protocol.

Quality of evidence:

Quality of evidence was assessed using GRADE methodology considering risk of bias assessment, imprecision, inconsistency, indirectness and publication bias into high, moderate, low and very low for each critical outcome.

Study	**1-** Perico et al. 2023[1]	**2-** Carlsson et al. 2023[2]	**3-** Izadi et al. 2022[3]	**4-** Ghodsi et al. 2012[4]
Study type	Randomized, placebo-controlled phase 1b/2a trial	Randomized double-blind placebo-controlled study	Randomized triple-blinded, placebo-controlled clinical trial	Double-blind placebo controlled clinical study
No of patients SC group/control group	12/4	Part A: 9 (To assess safety) Part B: 10/5	11/10	Type I-30 Type-II-26
Countries and setting:	Ireland, Italy and United Kingdom	Karolinska University Hospital, Stockholm, Sweden	Royan Institute, Tehran, Iran	Tehran University
Duration of study Follow up (post intervention):	18 months	12 months	Between July 2015 and January 2020	6 and 12 months
Method of assessment of disease condition:	ECG, FBG, HbA1c, GFR estimation by CKD-EPI and modification of Diet in Renal Disease	Ophthalmological examination, MMTTs to assess β cell function, C-peptide analysis, Exogenous insulin requirement	Fasting blood sugar (FBS), two-hour postprandial glucose test (2hpp), C-peptide, serum levels of Glycated hemoglobin (HbA1c), daily dose of injected EI, and lability index (LI).	Patients checked for viral infections including HCV, HBV, HIV, and urogenital infections before the final enrollment. Data for FBS, HbA1c, fasting serum c-peptide, CBC, liver function tests, lipid profile tests and U/A) were collected
Inclusion criteria:	• Age between 40 - 85 years with type 2 DM for 3 years or more, • Urine albumin-to- creatine	• Diagnosis of type 1 diabetes <2 years before enrolment, age 18-40 years and fasting plasma C-peptide concentration >0.12	Evaluated fasting C-peptide level ≥ 0.3 nmol/L and presence of at least one of three autoantibodies against	• Thirty patients with type 1 diabetes and twenty-six with type 2 diabetes

	ratio ≥88mg/g in a spot morning urine sample • eGFR 25-55 ml/min per 1.73 m^2 by CKD-EPI equation on two or more consecutive measurements at least 30 days apart with in the past 6 months A documented eGFR decline of ≥10 ml/min per 1.73 m^2 over the past 3 years or documented rate of eGFR decline ≥5 ml/min per 1.73 m^2 per year on the basis of 3 or more consecutive readings at least 90 days apart with in the past 18 months upto the date of consent, or an intermediate or high 5-year risk of progression to ESFK on the basis of validated Tangri 4-variable kidney failure risk equation for patients with CKD stage 3-5.	nmol/l.	pancreatic β cells (islet cell antibody [ICA], glutamic acid decarboxylase antibody [GADA], or insulinoma associated-2 antibody [IA-2A]).	were selected according to the on following criteria Age range between 10-60 years old, duration of the disease up to 20 years, blood glucose under 15mmol/l (270 mg/dl).
Exclusion criteria:	• Resting systolic BP ≥150 mm Hg and diastolic BP ≥90 mm Hg in a clinical setting, despite treatment with three antihypertensive agents of	BMI >30 kg/m^2, weight 100 kg, unstable cardiovascular status, active and chronic infections such as tuberculosis, HIV, hepatitis B or C or treponema pallidum	Pregnancy or breastfeeding; cancer; any acute or severe diseases (cardiac, pulmonary, hepatic, kidney, mental, or other	Acute vascular inflammation, acute thrombosis, recent retinal hemorrhage, pulmonary hypertension,

	different classes • HbA1c >75 mmol/mol • Fasting total cholesterol >7mmol/L • Fasting total glycerides >3.5 mmol/L • Positive screening test for anti-HLA antibodies (mean fluorescence intensity >1500)	infection, ongoing systemic immunosuppressive therapy, demyelinating disease, pregnancy or lactation (women), malignancy, glucose-lowering therapies other than insulin, a diagnosis of kidney disease defined as an eGFR of less than 80 ml/min per 1.73 m2 body surface, proliferative retinopathy, or known hypersensitivity reaction to excipients (i.e. DMSO).	diseases); positive test results for human immunodeficiency virus (HIV), human T-lymphotropic virus (HTLV), hepatitis B virus (HBV), hepatitis C virus (HCV), or cytomegalovirus (CMV); other immunodeficiencies; hyperesthesia; or history of severe ketoacidosis.	corpulmonale, bone marrow malignancy, end stage diseases, infections, and signs of refractory complications.
Recruitment/selection of patients:	Eligible patients were between age 40-85 years with type 2 DM for 3 years or more under a clinician with mandated responsibility for management to national guidelines. •	In part A of the study, 9 male participants, 18-40 years of age with newly diagnosed type 1 diabetes were included since studies of possible HLA immunization formed part of the safety analysis. Three participants were treated with low-dose ProTrans ($25x10^6$), followed by three participants receiving $100x10^6$ cells and three participants receiving $200x10^6$ cells. Based on the safety results in part A, women were allowed to participate in part B. Randomization in part B of	A total of 21 patients (age: 8 to 40 years) enrolled in this study. The patients were diagnosed with T1D according to diagnostic criteria and the ADA guidelines within six weeks before enrollment based on previous studies and were already under classic insulin therapy. Patients were enrolled between July 2015 and January 2018.	Fifty-six patients with type 1 (n=30) and type 2 (n=26) diabetes mellitus aged 10-58 years old (mean ± SD; 32.8 ± 16.3).

		the study was performed using a web-based randomization system, in blocks without stratification to either batch 1 ProTrans, batch 2 ProTrans or placebo treatment. All female participants were required to agree to use acceptable birth control (defined as methods with a failure rate of <1% per year when used correctly) to participate.		
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	Intravenous administration of Allo BM Mesenchymal stromal cell (80 million cells)	Intravenous administration of Allo WJ Mesenchymal stromal cell (200 million cells)	Participants were randomly assigned to receive either two doses of 1×10^6 autologous MSCs per kilogram of the patient's body weight or placebo at weeks 0 and 3	Fetal liver-derived cell suspension at the dosage of approximately 35-55×10^6 cells (7-11×10^6 $CD34^+$ HSCs) in 5 ml of normal saline intravenously Participants in placebo group received 5 ml of normal saline intravenously
Outcomes reported with time points	FBG, HbA1c, adverse events	Baseline C-peptide	Treatment-related adverse events and hypoglycemic episodes. Fasting blood sugar (FBS), two-hour	• No significant differences in demographic variables were observed between

			postprandial glucose test (2hpp), C-peptide, serum levels of Glycated hemoglobin (HbA1c), daily dose of injected EI, and lability index (LI).	type 1 and type 2 diabetic patients. • None of the patients became insulin free over the first year after transplantation. • In both type one and type two diabetes groups, the level of serum c-peptide did not change significantly within the groups or between them. In type 1 diabetes group, by the 6th month of follow up HbA1c significantly decreased compared to baseline
Funding	EU-Horizon 2020 Framework Programme grant 634086	NextCell Pharma, Stockholm, Sweden,	Royan Institute [code: 94000019]; and the Iranian Vice-Presidency for Science and Technology, Council for Development of Stem Cell Sciences and Technologies	• Details not given
Study	**5-** Zang et al. 2022[5]	**6-** Wu et al. 2022[6]	**7-** Mirzaei et al. 2021[7]	• **8-** Estrada et al. 2019[8]

Study type	Double-blinded, randomized, placebo-controlled phase II trial	Randomized controlled open-label clinical study	Randomized single blinded trial	• Prospective, randomized controlled trial.
No of patients SC group/control group	45/46	14/15	10/10	• 13/10
Countries and setting:	First Medical Center of Chinese PLA General Hospital (PLAGH; Beijing, China)	Hospital, China, USA	Urology Clinic of Bahonar Hospital, Kerman	• Argentina, Hospital
Duration of study Follow up (post intervention):	9, 20, 32, and 48 weeks	8-year follow-up	6 months	• 12 months
Method of assessment of disease condition:	HbA1c, total insulin dose, daily insulin requirement	Body mass index, fasting plasma glucose, C-peptide and HbA1c and C-peptide/glucose ratio (CPGR)	FBS, HbA1c	• Fasting plasma glucose, C-peptide, and HbA1c, C-peptide/glucose ratio (CPGR).
Inclusion criteria:	• Aged between 20 and 65 years; • Diagnosed with T2DM for < 20 years (HbA1c levels between 7.0% and 12.0%, inclusive; • Inadequately controlled by stable insulin therapy (0.5–1.0 U/kg/day) with metformin for ≥ 3 months; With fasting C-pep tide levels of ≥ 1 ng/mL; and (5) with a	Age 18-40 years, history of T1D 2 years and 16 years, HbA1c 7.5% (58 mmol/mol) and 10.5% (91 mmol/mol), fasting serum C-peptide <0.1 pmol/ml and daily insulin requirement <100 IU.	• Patients aged 50-70 years with erectile dysfunction Non-respondents to the common treatments of erectile dysfunction including PDE5I.	• Age 45 to 65 years, provided written informed consent, were mentally stable and able to comply with the procedures of the study, clinical history compatible with T2DM, onset of T2DM disease at 40 years of age, T2DM duration 5 and 15 years at the time of

	body mass index (BMI) of 24–40 kg/m^2.			enrollment, basal C-peptide 0.5–2.0 ng/mL, HbA1c 7.5% and 11% before SMT, treated with SMT for four months prior to randomization with stable insulin and met form in doses over three months prior to randomization, HbA1c at 7.5 and 9.5% at randomization, and a total insulin daily dose (TDD) 100 units (U)/day at the time of randomization.
Exclusion criteria:	• Patients had ketonuria, tumors, serum creatinine levels < 175 μmol/L, previously diagnosed with myocardial infarction, current angina or heart failure, > 1 major vascular event, retinopathy that required laser treatment, malignant hypertension, an uncorrected endocrine disorder, occupations that	Patients with microalbuminuria, chronic renal dysfunction, proliferative and non-proliferative retinopathy, chronic liver dysfunction, pancreatitis, abdominal aortic aneurysm and chronic viral infections were excluded.	• -	• Patients were not eligible if their body mass index (BMI) was >35 kg/m^2, their insulin requirement was >100 U/day, HbA1c was >9.5% at the time of randomization, or status of type 1 (GAD-65) glutamate decarboxylase was

	precluded insulin therapy, severe concurrent illness that limited life expectancy, inadequate understanding of the study protocol, drug abuse, planning pregnancy, and an allergic constitution			seropositive.
Recruitment/selection of patients:	• Patients aged between 20 and 65 years diagnosed with T2DM for < 20 years	Twenty-one patients were randomized to either the stem cell transplantation (SCT)-treated group (disease duration mean, 9.2±4.6 years, range, 2-16 years and age of onset mean, 18.3±5.1years, range, 5-28 years) or the control group (disease duration mean, 7.0±3.2 years, range, 2-13 years and age of onset mean, 20.4±3.2 years, range, 13-27 years)	• 20 diabetic patients aged 50-70 yrs with erectile dysfunction	• BMASCs were harvested under local or general anesthesia using multiple bone marrow aspirations from both iliac crests according to standard operating procedure.
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• Intravenous infusion of 1×10^6/kg UC-MSCs (100 mL) or the same volume and appearance of placebo (UC-MSCs suspension liquid composed of saline with 3% human albumin and 0.5 mL multivitamins) at the elbow joint three times with an interval of 4 weeks and then discharged after 24 h of observation without	Umbilical cord MSC plus a BM-MNCs transplantation In SCT group, a total of $1.10\pm0.22\text{x}10^6$ MSCs/kg and $0.61\pm0.26\text{x}10^{10}$ aBM-MNCs/kg was infused.	Intracavernosal injection of $50\text{-}60\text{x}10^6$ MSCs diluting with 0.9% saline injected to the patients of intervention group • Control: Normal saline into corpus cavernosum	Hyperbaric oxygen therapy (HBOT)+ SC + standard medical treatment (SMT) (Intervention group) ASCs were infused into the main arterial supply of the pancreas. • SMT (Control

	any adverse events.			group)
Outcomes reported with time points	Overall, 13.5% (5/37) patients became insulin-free at 8–24 weeks (12± 7.6 weeks) after UC-MSCs transplantation and remained insulin-free without re-use for 37.2± 15.2 weeks. No patient in the placebo group became insulin-free. HbA1c levels declined with a maximum decrease observed at 9 weeks after treatment, and slightly increased at 20, 32, and 48 weeks of follow-up. • The fasting C-peptide levels in the UC-MSCs group did not significantly change after treatment.	Chronic diabetes complications such as diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN) and diabetic retinopathy (DRP) safety, islet function and metabolic control	Mean value of FBS at the baseline and 6 months after the intervention were 118±9.5 and 117±9.3 in the intervention group and 116±9.3 and 118±9.4 in the control group. Mean value of HbA1c at the baseline and 6 months after the intervention were 6.8±2.1 and 6.7±2 in the intervention group and 6.7±2.05 and 6.8±2.15 in the control group.	• Plasma glucose levels and HbA1c, and β-cell function measured by basal C-peptide levels. • BMI was significantly higher in the intervention group: 27.0 + 4.0 versus 23.1 + 2.5, respectively. HbA1c was significantly lower in the intervention group compared with the control group throughout follow-up, with the most significant differences at 180 days: 6.7±1.0% versus 8.2±1.0% in intervention versus control groups, respectively, p = 0.0025. At 365 days, HbA1c percentages were 7.3 + 0.9% versus 8.0 ± 0.7% in intervention and

				control groups, respectively, p = 0.0366.
Funding	This study was supported by grants from the National Natural Science Foundation of China (Nos. 81700679 and 81700680), the National Key Research and Development Program of China (No. 2017YFC0908402), and the 863 Projects of the Ministry of Science and Technology of China (No. 2013AA020105).	This study was supported by the Natural Science Fund of Fujian Province (2020J011131), Science and technology innovation joint fund project in Fujian Province (2019Y9004), Startup fund for scientific research of Fujian Medical University (2017XQ1205) and 900th Hospital of the Joint Logistic Support Force Fund (2018J07).	Kerman University of Medical Sciences	• This study was supported by Hospital de Alta Complejidad de Formosa, Argentina.
Study	**9-** Sood et al. 2017[9]	**10-** Packham et al. 2016[10]	**11-** Hu et al. 2016[11]	• **12-** Cai et al. 2016[12]
Study type	Single blinded Randomized clinical trial	Randomized, single-blinded placebo-controlled study	Phase I/II randomized controlled study	• Single Centre Randomized Control open label trial
No of patients SC group/control group	21/7	20/10	31/30	• 21/21
Countries and setting:	India	Australia, Hospital	China	• China, Florida
Duration of study Follow up (post intervention):	6 months	60 weeks	36 months	• I year
Method of assessment	C-peptide assay; HOMA-IR	GFR estimation using the 4-	Fasting plasma glucose	• Measurement of

of disease condition:	and HOMA-B; Reduction in Insulin dose; subjects who showed reduction of insulin requirement of more than 50% from baseline requirement were regarded as responders; and reduction in HbA1c.	variable Modification of Diet in Renal Disease (MDRD). Urinary albumin and protein, urinary albumin: creatinine, urinary protein: creatinine ratios, creatinine clearance	(FPG), postprandial plasma glucose (PPG), C-peptide/glucose ratio	serum levels of GAD antibodies (GADA) at time of onset.
Subgroup analysis within study	-	-	-	• -
Inclusion criteria:	• Patients with T2DM between 30 and 70 years of age; • failure to triple OHA (Oral hypoglycaemic agents) and on stable doses of Insulin for at least 3 mo; • On Vildagliptin, Pioglitazone and Metformin for at least 3 mo along with Insulin to maintain euglycemia; • HbA1c of 6.5%-7.5%; • Insulin requirement ≥ 0.4 IU/kg per day; and Glutamic acid decarboxylase (GAD 65) antibody negative status.	• The study population was male and female patients ≥45 and ≤85 years old with type 2 diabetes and advanced diabetic nephropathy (e.g. eGFR 20–50 ml/min/1.73 m^2) receiving a stable, standard of care therapeutic regimen of the maximum tolerated recommended dose of an angiotensin converting enzyme inhibitor (ACEi) or a angiotensin 2 receptor blocker (ARB) for at least 3 months prior to screening. Patients who, in the opinion of the investigator and, in accordance with the current consensus recommendations in Australia would be unlikely	Patients of either sex, aged 18-60 years, with a clinical and laboratory diagnosis of T2DM according to the criteria outlined by the American Diabetes Association	• Inclusion criteria were both sexes, age 18–40 years, history of T1D ≥2 and ≤16 years (a time frame selected to al low confirmation of T1D diagnosis and to avoid the potentially confounding ef fects of long-standing diabetes complications), HbA1c ≥7.5% (58 mmol/mol) and ≤10.5% (91 mmol/mol), fasting se rum C-peptide, <0.1 pmol/mL, and daily insulin requirements, <100 IU.

		candidates for kidney transplant were included. Women of childbearing potential who were surgically sterile or agreed to use contraception were eligible to participate in the study.		
Exclusion criteria:	• Patients with T1DM or secondary diabetes; • Patients with serum creatinine > 1.5 mg/dL; • Abnormal liver function tests (defined as value of transaminases > 3 times the upper value of normal or serum bilirubin higher than normal for the reference value of the laboratory); • History of pancreatitis; • Seropositivity for HIV, HBsAg and HCV; • History of myocardial infarction or unstable angina in the previous 3 mo; • History of malignancy; • Patients with active infections; and	• New York Heart Association Class III or IV heart failure and myocardial infarction or stroke within 6 months of screening. For Complete eligibility criteria check supplemental Study Protocol	Any malignancies; pancreatic congenital anomaly; positive serology for human immunodeficiency virus (HIV), hepatitis B (HBV) or hepatitis C (HCV); underlying hematologic, nephrologic, cardiac, psychiatric, or hepatic disease; pregnancy; any acute or chronic infection; and any other endocrine and metabolic disease, including hyperthyroidism, hypercortisolism, acromegaly or chromaffin tumor	• Patients with chronic renal dysfunction, proliferative retinopathy, chronic liver dysfunction, pancreatitis, abdominal aortic aneurysm, and chronic virus infections were excluded.

	• Female patients who are pregnant or lactating			
Recruitment/selection of patients:	A total of 130 patients were screened from June 2010 to May 2012, out of which 42 were eligible. They were randomly divided into two groups and a total of 28 cases were included finally divided in 4 arms with 7 patients in each arm. Arm IV is control arm. •	• Male and female patients ≥45 and ≤85 years old with type 2 diabetes and advanced diabetic nephropathy	A total of 87 patients met the inclusion criteria and, following an interview, 64 patients were enrolled. Although 64 patients with T2DM were initially enrolled, 2 patients in group II and one patient in group I withdrew at the start of follow-up due to immigration to other distant city and a lack of availability. The remaining 61 patients completed the entire study and their data were analyzed.	• Among 75 patients screened, 42 were finally enrolled and randomized into an SCT group (n=21 receiving UC-MSCs + BM-MNCs trans plantation and standard clinical treatment) or a continued standard clinical treatment (control) group (n = 21) between July and December 2009 and were observed until December 2010 at 3-month intervals.
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	Bone marrow mononuclear cells characterized by CD34+ count using different routes of administration Intervention group: Group I: 4.9±3.10 x 10^8 Group II: 12.04±4.84 x 10^8	• IV infusion • BMMNCs • Patients were randomized to receive one of two rexlemestrocel-L doses or placebo in a 2:1 ratio using a sequential, escalating dose cohort paradigm: cohort 1: 150 × 10^6 [n = 10] or	Thawed UCB cells were infused through a peripheral intravenous line followed by 1 year of supplementation with vitamin D and docosahexaenoic acid (DHA).	• 60–80 mL BM-MNCs (106.8 x 3 10^6/kg) plus 30–50 mL UC-MSCs (1.1 x 10^6/kg) were sequentially infused within 30 min through supraselective pancreatic artery

	Group III: 6.88 ± 2.30 x 10^8	placebo [n = 5]; and cohort 2: 300 × 10^6 [n = 10] or placebo [n = 5].		canulation
Outcomes reported with time points	• An increase in area under C-peptide response curve among all groups but the values remained statistically non-significant. • No significant improvement in Insulin sensitivity indices of HOMA IR and HOMA B • A progressive and consistent decrease in fasting and post prandial plasma glucose leading to decrease in Insulin doses was noted in group I and group II statistically significant at 6 months of follow-up. None of them reached the primary objective of 50% reduction in Insulin dose. HbA1c levels showed reduction or were	• Reduction in insulin requirement by ≥50%, while maintaining HbA1c <7%, and the secondary end points were a change in weight, HbA1c, and stimulated C-peptide levels compared to the baseline	• C-peptide decline and insulin use • Fasting plasma glucose β-cell function	• The AUCC-Pep increased 105.7% from basal (6.6 6 6.1 to 13.6 6 8.1 pmol/mL/180 min, P = 0.00012), with 15 of 21 patients (71.4%) showing increased levels at 1 year • HbA1c levels decreased significantly at 3, 6, 9, and 12 months • FBG was unchanged during the follow up period in the control group, whereas it decreased significantly in the SCT group at 3, 6, 9, and 12 months.

	maintained at the baseline level and this was observed despite tapering of Insulin dosages across all groups.			
Funding	• Indira Gandhi Medical College, Shimla	• This study was sponsored by Mesoblast, Inc.	• No Information	• Fujian Province
Study	• **13-** Nasli-Esfahani et al. 2015[13]	• **14-** Bhansali et al. 2014[14]	• **15-** Haller et al. 2013[15]	• **16-** Hu et al. 2013[16]
Study type	• Double blind randomized controlled clinical trial	• Randomized, single-blinded placebo-controlled study	• Open-label, 2:1 randomized study	• Randomized controlled double-blind trial
No of patients SC group/control group	• 30/26	• 11/10	• 10/5	• 15/14
Countries and setting:	• Iran	• India, Hospital	• Florida	• Stem Cell Centre of the Affiliated Hospital of the Medical College, Qingdao, China
Duration of study Follow up (post intervention):	• 3 yrs	• 12 months	• 3 months, 6 months, and 1 year.	• 24 months with 3 months follow up
Method of assessment of disease condition:	• Assessment of diabetes retinopathy and the results were reported as normal, Non–Proliferative Diabetic Retinopathy (NPDR), and Proliferative Diabetic Retinopathy (PDR).	• Clinical assessment regarding glycemic control, micro- and macro vascular complications, body mass index, waist circumference, ankle brachial index, electrocardiography.	• Complete blood count, HbA1C beta cell autoantibodies, vitamin D studies, serum cytokines	• All patients received extensive physical and laboratory examinations, including age, gender, height, weight, diabetes

	• As for the assessment for nephropathy, 24-hours urine was collected and tested for proteinuria and the results were reported as no albuminuria, micro-albuminuria and macro-albuminuria • Ischemic Heart Disease (IHD), • HbA1c levels			duration, dose of insulin used, whole blood cell counts, liver and renal function tests, cardiac enzyme, cardiac troponin, serum electrolytes, serum lipids, blood coagulation function, microalbuminuria, cancer screening test and glutamic acid decarboxylase antibody (GADA) test, were recorded at baseline and during the follow-up period every 3 months. Plasma glucose was measured by enzymatic (glucose oxidase/ peroxidase) colorimetric method. C-peptide was tested by the C-peptide response test (Roche Diagnostics, Germany; normal

				range: 1.1-4.4 ng/mL). • Postprandial C peptide. • HbA1c (Bio-Rad D10, USA; normal range: 3.9% 6.1%) and the C-peptide/glucose ratio (CPGR) were also examined.
Subgroup analysis within study	• -	• -	• -	• -
Inclusion criteria:	• -	• Patients with T2DM, age ranging from 30 to 70 years, having diabetes for ≥5 years with failure of triple oral antidiabetic drugs in optimal doses (metformin 2 g per day, glimepiride 4 mg per day, pioglitazone 15 mg per day) and requiring insulin (≥0.4 IU/kg per day) for at least 1 year to achieve optimal glycemic control. Before the randomization, patients were on stable doses of vildagliptin 100 mg per day + metformin 2 g per day (Galvus Met,	• Children with type 1 diabetes older than 1 year of age.	• Patients of both sexes, aged not exceeding 25 years, with a clinical and laboratory diagnosis of T1DM according to the criteria of the American Diabetes Association and a diabetic duration not more than 6 months, fasting C-peptide ≥ 0.3 ng/mL.

		Novartis India, Mumbai, India), pioglitazone 15 mg per day (Pioglar, Ranbaxy, Mumbai, India), and insulin (≥0.4 IU per kg per day) (Human Mixtard, Actrapid, or Insulatard, Novo-Nordisk, Bangalore, India) for at least 3 months with glycated hemoglobin (HbA1c) of 7.5%.		
Exclusion criteria:	• -	• Type 1 diabetes mellitus, glutamate decarboxylase 65 (GAD-65) seropositive status, serum creatinine >1.5 mg/dl, abnormal liver function tests, active infections, malignancy, or acute coronary syndrome in the previous 3 months.	• -	• Patients with malignancy; any acute or chronic infection; pregnancy; positive serology for human immunodeficiency virus, hepatitis B or C; underlying hematologic, nephrologic, cardiac, psychiatric, or hepatic disease; mental disorders; inborn or adaptive immunodeficiency and hypersensitivity were excluded.
Recruitment/selection of patients:	• 56 patients with type one (n=30) and type 2 (n=26) diabetes who had previously participated in a	• Out of 120 patients screened between August 2009 and December 2009, 26 patients were eligible as	• Children with type 1 diabetes older than 1 year of age and for whom autologous UCB	• Twenty-nine patients with newly onset T1DM were randomly divided

	double blind randomized controlled clinical trial in 2007 (Ethical Code: 0089 and IRCT number: 138811071414 N10), had been visited at the 6th and the 12th months after injection. 44/56 signed an informed consent and agreed to participate.	per inclusion criteria and 21 were finally randomized into two groups.	were recruited for participation	into two groups, patients in group I were treated with WJ-MSCs and patients in group II were treated with normal saline based on insulin intensive therapy.
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	• Intervention group-Fetal liver-derived cell suspension at the dosage of approximately 35-55×10^6 cells (7-11 × 10^6 $CD34^+$ HSCs) in 5 ml of normal saline intravenously. Participants in placebo group received 5 ml normal saline intravenously	Auto BM SCTs through a targeted approach and after 12 weeks second dose through antecubital vein with G-CSF. Control group- Sham Procedure •	• Thawed UCB cells were infused through a peripheral intravenous line followed by 1 year of supplementation with vitamin D and docosahexaenoic acid (DHA).	Allo WJ MSCs 2.6 ± 1.2 × 10^7 (1.5 - 3.2 × 10^7) •
Outcomes reported with time points	• There were no significant differences in the incidence or progression of diabetes micro vascular complications in patients who had either undergone fetal liver-derived cell suspension allotransplantation or received placebo compared to the baseline. One case of meningioma was reported.	Reduction in insulin requirement by ≥50%, while maintaining HbA1c <7%, and the secondary end points were a change in weight, HbA1c, and stimulated C-peptide levels compared to the baseline	• C-peptide decline and insulin use	• The difference in FPG was not significant between two groups. • There was a significant dif ference in HbA1c between the two groups at the sixth month and at subsequent time

				points (P < 0.05). Mean CPGR levels increased progressively in group I patients during the entire follow-up period, but decreased gradually in group II patients. The difference between the two groups was significant (P < 0.05). In 7/14 patients, insulin was increased by more than 50% of the baseline; in the 7 remaining patients, insulin was slightly increased by about 15-45%. The difference between the two groups was significant (P < 0.001).
Funding	• -	Defence Research and Development Organization (DRDO), India	• Supported by the Juvenile Diabetes Research Foundation (JDRF) innovative grant 1-2005-362, JDRF center grant 4-2007-1065, National Institutes of Health (NIH) contract	• This work was supported by Human Umbilical Cord Mesenchymal Stem Cell Bank, Shandong Province, China.

			M01RR00082, and NIH grant 1R21DK077580-01. The University of Florida CTSI is supported in part by NIH award UL1TR000064 from the National Center for Advancing Translational Science. DHA was donated by Martek Biosciences Corporation	
Study	• **17-** Huang et al. 2005[17]	**18-** Bhansali et al. 2016[18]	• **19-** Skyler et al. 2015[19]	• **20-** Carlsson et al. 2015[20]
Study type	• Prospective controlled randomized clinical trial	Randomized, single-blinded, placebo-controlled stud	• Multicentre, randomized, single-blind, placebo-controlled, sequential trial- Type 2 Diabetes	• Open, single-center, randomized pilot
No of patients SC group/control group	• 14/14	20/10 (three groups 10 in each)	• 61	• 10/10
Countries and setting:	• Institute of Hematology & Hospital of Blood Diseases, Chinese Academy of Medical Sciences & Peking Union of Medical College.	Postgraduate Institute of Medical Education and Research, Chandigarh, India	• U.S.	• Uppsala University Hospital, Sweden
Duration of study Follow up (post intervention):	• February 2003 to June 2004	12 months	• 12 weeks	• One year
Method of assessment	Assessment of pain-free	Glycemic control, micro-, and	• Subjects were	• Maintained fasting

of disease condition:	walking distance ABI (ankle-brachial pressure index) and blood flow (height of wave amplitude) of 10 toes digital subtraction angiography 1 week before and 12 weeks after treatment. The angiographic scores • Fasting plasma glucose level	macrovascular compli cations, HbA1c level, Glucagon-stimulated C-peptide test, C-peptide estimation, Fasting plasma insulin	randomized to receive one of the following three rexlemestrocel-L doses or placebo in a 3:1 ratio using a sequential, escalating dose cohort paradigm: cohort 1, 0.3x3 10^6/kg (n =15) or placebo (n = 5); cohort 2, 1.0x 10^6/kg (n = 15) or placebo (n = 5); and cohort 3, 2.0x 10^6/kg (n = 15) or placebo (n =5).	C-peptide and evoked C-peptide response to a mixed-meal tolerance test (MMTT), blood glucose control by HbA1c, changes in insulin doses per kilogram, and changes in levels of autoantibodies to b-cells (GAD65 and IA2 anti bodies
Subgroup analysis within study	-	-	• -	• -
Inclusion criteria:	Diabetic patients with proven CLI, but without hyper-coagulable states or gangrene above the ankle and/or severe coronary, cerebral, and renal vascular disease, were eligible for participation in this trial.	• Patients of either sex with T2DM, aged between 30 and 60 years with duration of diabetes ≥5 years, and failure to achieve HbA1c ≤7.5% (≤58.0mmol/mol), while receiving triple oral anti-diabetic drugs in optimal doses along with insulin (≥0.4 IU per Kg per day) for the last 6 months. Prior to randomization, patients were on stable doses of vildagliptin, metformin, pioglitazone and insulin (≥0.4 IU per Kg per day) during run-in-period for at least 3	• Women of child bearing potential who were surgically sterile or agreed to use contraception during the entire study were eligible to participate.	• 18–40 years of age with type 1 diabetes diagnosed, 3 weeks before enrolment and with a stimulated C-peptide level .0.1 nmol/L. None of the patients were allowed to be pregnant; have BMI .30; have tested positive for HIV, viral hepatitis B or C, or Treponema pallidum; be immune sup pressed; or have known or previous

		months with HbA1c ≤7.5% (≤58.0mmol/mol).		malignancy. All participants were given oral and written information about the study and signed a written consent prior to inclusion to the study. The study was approved by the Uppsala ethics board, and the reported investigations were performed in accordance with the principles of the Declaration of Helsinki as revised in 2000
Exclusion criteria:	-	• Patients with T1DM, glutamate decarboxylase-65 seropositive, abnormal liver and renal function tests, active infections, malignancy, or acute coronary syndrome in the past 3 months were excluded.	• C-peptide level ≤0.8 ng/mL, systolic blood pressure ≥170 mmHg, or diastolic blood pres sure ≥110 mmHg; type 1 diabetes, di abetes resulting from pancreatic injury, or secondary forms of diabetes; acute metabolic diabetes complications (e.g., ketoacidosis, hyperosmolar coma)	• -

			within 6 months of screening; severe hypoglycemia (defined as requiring third-party assistance) or repeated or frequent hypoglycemic episodes within 1 month before screening; insulin therapy within 6months of screening except if used transiently for <7 days for inter current illness; New York Heart Association class III or IV heart failure; myocardial infarction or stroke within 6 months of screening; diagnosed and/or treated malignancy (except for treated basal cell or squamous small cell carcinoma of the skin with no evidence of recurrence); and presence of ≥20% anti-HLA antibody f low panel reactive antibody (PRA) class I or II and/or antibody specificities to donor HLA antigens.	
Recruitment/selection	Twenty-eight diabetic patients with proven CLI, but	• Thirty patients of T2DM with duration of disease ≥	• The study population included ~60 adults ≤80	• Twenty-six patients newly diagnosed

of patients:	without hypercoagulable states or gangrene above the ankle and/or severe coronary, cerebral, and renal vascular disease	5yrs, receiving triple oral anti-diabetic drugs along with insulin (≥0.4 IU per Kg per day) with HbA1c ≤7.5% (≤58.0mmol/mol) were randomized to receive ABM-MSCs or ABM-MNCs through targeted approach and a sham procedure (n=10 each)	years of age with type 2 diabetes (HbA1c ≥7.0% to <10.5% [≥53 to <91 mmol/mol] at screening) who were receiving a stable therapeutic dose of metformin either alone or in combination with one other oral antidiabetic medication (except a thiazolidinedione) for at least 3 months before screening.	with type 1 diabetes between April 2010 and May 2012 fulfilled screening criteria and 20 patients participated in the study. Two of the total 20 patients in the study (one in the MSC group and one in the control group) withdrew during the 1-year study period
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	The control patients received an intravenous injection of 90-200 μg/day prostaglandin E1. In transplant group, the patients received treatment with 600 g/day recombinant human G-CSF by subcutaneous injection for 5 days to mobilize stem/progenitor cells. Meanwhile, a perfusion of 10,000 units/day heparin for 5 days by intravenous drip was used to avoid the possible risks of embolism	• BMMSCs were infused at a dose of one million cells per Kg body weight, whereas BMMNCs at a dose of approximately one billion cells per patients	One intravenous (IV) infusion of MPCs (rexlemestrocel-L; Mesoblast Inc.) 0.3 3 10^6/kg (n =15), 1.03 10^6/kg (n =15), or 2.03 10^6/kg (n = 15) or placebo (n = 16). 45/16 Allo MPCs • (.3-2 million cells /kg)	• Three to four weeks after bone marrow harvest, 2.1–3.6 x 10^6 autologous cells/kg (median 2.75 x 10^6 cells/kg) were given as one single intravenous 20-min infusion without premedication.

	because of a G-CSF induced increase of circulating blood cells. Then, 300 ml suspension of blood circulating PBMNCs were collected from patients treated with G-CSF, through a Version 4 blood-cells separator and concentrated to 1x 10^8 mononuclear cells/ml. Superfluous cells were frozen in liquid nitrogen for further use. Three hours later, each diseased lower limb was intramuscularly injected (40 sites, 3 1–1.5 cm deep, 7.5 x10^8 mobilized PBMNCs per site) into thigh and leg with a total of 3x10^9 mobilized PBMNCs.			
Outcomes reported with time points	• The scale of rest pain decreased from 3.86 ± 0.36 to 1.07 ± 0.92 points (P<0.001) with a pain-free walking distance from 0.0± 0.0 to 306.4 ± 289.1 m (P=0.001). Only six patients recovered normal sleep in the control group at 12	• Reduction in insulin requirement by ≥50% from baseline, while maintaining HbA1c ≤7.5% (≤58.0 mmol/mol) were randomized to receive ABM-MSCs or ABM-MNCs through targeted approach and a sham procedure (n=10 each). • Secondary end points	Compared to placebo, a single IV infusion of rexlemestrocel-L reduced HbA1C at all time points after week 1. The adjusted least squares mean 6 SE dose-related differences in HbA1c from placebo in the rexlemestrocel-L	• During first year C-peptide peak values and area under the curve was preserved or even increased in MSC treated patients in contrast to control arm. •

	weeks. After 12 weeks of treatment, the mean fasting plasma glucose level significantly decreased from 9.00 ± 0.95 mmol/l at baseline to 6.12 ± 0.97 mmol/l (P<0.001) in the transplant group but slightly decreased from 8.42 ± 1.20 mmol/l at baseline to 7.82 ± 1.59mmol/l (P=0.065) in the control group.	included change in weight, HbA1c, metabolic indices including C-peptide and insulin sensitivity as compared to the baseline. •	groups ranged from -0.1± 0.2% (-1.1±2.2 mmol/mol) to -0.4± 0.2% (4.4±2.2 mmol/mol) at 8 weeks and from 0.0± 0.25% to -0.3±0.25% (-3.3 ± -2.7 mmol/mol) at 12 weeks (P < 0.05 for 2.0 x 10^6/kg dose at 8 weeks).	
Funding	• Ministry of Science & Technology of China and a grant from the China Medical Board of New York	• Endocrine Society of India	This study was sponsored by Mesoblast Inc. and designed by the sponsor with input from the authors and the contract research organization (CRO) Medpace, Inc. (Cincinnati, OH).	• Academic grants from the Swedish Research Council

ix. List of excluded studies

S. No.	Author et al. Year	Title of the study	Reason for exclusion
1	Liu et al. 2013	Amniotic stem cell transplantation therapy for type 1 diabetes: a case report.	Observational study design
2	Koh et al. 2013	Successful treatment of brittle diabetes following total pancreatectomy by islet allotransplantation: a case report.	Observational study design
3	Zhang et al. 2019	Circulating Tissue Factor-Positive Procoagulant Microparticles in Patients with Type 1 Diabetes.	Observational study design
4	Araujo et al. 2020	Allogenic Adipose Tissue-Derived Stromal/Stem Cells and Vitamin D Supplementation in Patients with Recent-Onset Type 1 Diabetes Mellitus: A 3-Month Follow-Up Pilot Study.	Non-randomized study design
5	Dubsky et al. 2019	Impact of severe diabetic kidney disease on the clinical outcome of autologous cell therapy in people with diabetes and critical limb ischaemia.	Non-randomized study design
6	Zhang et al. 2018	Comprehensive assessment of T-cell repertoire following autologous hematopoietic stem cell transplantation for treatment of type 1 diabetes using high-throughput sequencing.	Non-randomized study design
7	Walicka et al. 2018	Lack of persistent remission following initial recovery in patients with type 1 diabetes treated with autologous peripheral blood stem cell transplantation.	Non-randomized study design
8	Ye et al. 2017	Immune response after autologous hematopoietic stem cell transplantation in type 1 diabetes mellitus.	Non-randomized study design
9	Ulyanova et al. 2016	Leptin Level in Patients with Type 2 Diabetes Mellitus after Fetal Pancreatic Stem Cell Transplant.	Non-randomized study design
10	Dou et al. 2015	A follow-up study on autologous bone marrow mononuclear cells transplantation for critical lower arteriosclerosis obliterans in diabetic patients	Non-randomized study design
11	Gu et al. 2014	Autologous hematopoietic stem cell transplantation and conventional insulin therapy in the treatment of children with newly diagnosed type 1 diabetes: long term follow-up.	Non-randomized study design
12	Zhang et al. 2012	Acute response of peripheral blood cell to autologous hematopoietic stem cell transplantation in type 1 diabetic patient.	Non-randomized study design
13	Dantas et al. 2023	Adipose Tissue-Derived Stromal/Stem Cells Transplantation with Cholecalciferol Supplementation in Recent-Onset Type 1 Diabetes Patients: Twelve Months Follow-Up.	Non-randomized study design
14	Lian et al. 2022	Effectiveness and safety of human umbilical cord-mesenchymal stem cells for treating type 2 diabetes mellitus.	Non-randomized study design

15	Elhusseiny et al. 2023	Mesenchymal Stem/Stromal Cells: mesenchymal stem cell therapy in diabetic kidney disease: evaluating safety and response predictors	Non-randomized study design
16	Jawale et al. 2022	Stem cell therapy for type1 diabetes with transplantation of stem cells into the Omental pouch, peritoneum, and blood, experimental study.	Non-randomized study design
17	Tootee et al. 2022	Clinical Outcomes of Fetal Stem Cell Transplantation in Type 1 Diabetes Are Related to Alternations to Different Lymphocyte Populations.	Non-randomized study design
18	Dantas et al. 2021	Adipose tissue-derived stromal/stem cells + cholecalciferol: a pilot study in recent-onset type 1 diabetes patients.	Non-randomized study design
19	Rios et al. 2021	Long-term Persistence of Allosensitization After Islet Allograft Failure.	Non-randomized study design
20	Lu et al. 2021	One repeated transplantation of allogeneic umbilical cord mesenchymal stromal cells in type 1 diabetes: an open parallel controlled clinical study.	Non-randomized study design
21	Mao et al. 2019	Efficacy of autologous bone marrow mononuclear cell transplantation therapy in patients with refractory diabetic peripheral neuropathy.	Non-randomized study design
22	Gu et al, 2018	Clinical benefits of autologous haematopoietic stem cell transplantation in type 1 diabetes patients.	Non-randomized study design
23	Ulyanova et al. 2018	Transforming Growth Factor Î²1 in Patients with Type 2 Diabetes Mellitus After Fetal Pancreatic Stem Cell Transplant.	Non-randomized study design
24	Al Demour et al. 2018	Safety and Potential Therapeutic Effect of Two Intracavernous Autologous Bone Marrow Derived Mesenchymal Stem Cells injections in Diabetic Patients with Erectile Dysfunction: An Open Label Phase I Clinical Trial.	Non-randomized study design
25	Wang et al. 2018	Autologous Mesenchymal Stem Cell and Islet Cotransplantation: Safety and Efficacy.	Non-randomized study design
26	Penaforte-Saboia Saboia et al. 2017	Microvascular Complications in Type 1 Diabetes: A Comparative Analysis of Patients Treated with Autologous Nonmyeloablative Hematopoietic Stem-Cell Transplantation and Conventional Medical Therapy.	Non-randomized study design
27	Snarski et al. 2016	Immunoablation and autologous hematopoietic stem cell transplantation in the treatment of new-onset type 1 diabetes mellitus: long-term observations.	Non-randomized study design
28	Thakkar et al. 2015	Insulin-secreting adipose-derived mesenchymal stromal cells with bone marrow-derived hematopoietic stem cells from autologous and allogenic sources for type 1 diabetes mellitus.	Non-randomized study design
29	Bhansali et al.	Efficacy and safety of autologous bone marrow	Non-randomized

	2014	derived hematopoietic stem cell transplantation in patients with type 2 DM: A 15 months follow-up study.	study design
30	Mesples et al. 2013	Early immunotherapy using autologous adult stem cells reversed the effect of anti-pancreatic islets in recently diagnosed type 1 diabetes mellitus: preliminary results.	Non-randomized study design
31	Zhao et al. 2012	Reversal of type 1 diabetes via islet Î² cell regeneration following immune modulation by cord blood-derived multipotent stem cells.	Non-randomized study design
32	Hu et al. 2012	Long term effects of the implantation of autologous bone marrow mononuclear cells for type 2 diabetes mellitus.	Non-randomized study design
33	Dantas et al. 2020	Or: Allogenic adipose-derived mesenchymal stem cells (ASCS) and vitamin d supplementation in patients with recent-onset type 1 diabetes mellitus: A 6-month follow-up pilot study	Non-randomized study design
34	Wei et al. 2020	Autologous Bone Marrow Mononuclear Cell Transplantation Therapy Improved Symptoms in Patients with Refractory Diabetic Sensorimotor Polyneuropathy via the Mechanisms of Paracrine and Immunomodulation: A Controlled Study	Non-randomized study design
35	Shi et al. 2016	Efficacy and safety of autologous marrow stem cell transplantation in patients with diabetic peripheral neuropathy: A double-blind, randomly paired trial	Non-randomized study design
36	Dubois-Laforgue, Laforgue et al. 2015	Autologous stem cell transplantation in new-onset type 1 diabetes: Mixed results	Non-randomized study design
37	Giannopoulou et al. 2014	Effect of a single autologous cord blood infusion on beta-cell and immune function in children with new onset type 1 diabetes: A non-randomized, controlled trial	Non-randomized study design
38	ChiCTR-ONRC et al. 2019	Autologous bone marrow stem cells transplantation for diabetes mellitus	Non-randomized study design
39	Madani et al. 2020	Placental mesenchymal stem cell transplantation for treatment of T1DM: A pilot study	Non-randomized study design
40	Adorable-Wagan, Wagan et al. 2014	The safety of bone-marrow derived mesenchymal stem cells in patients with type 2 diabetes mellitus	Non-randomized study design
41	Khan et al. 2019	Stem Cell-Based Therapies: A New Ray of Hope for Diabetic Patients	Duplicate
42	Kapoor et al. 2018	Randomized case control study for the clinical evaluation of stem cell therapy in patients with type 1 diabetes-one year follow up	Conference abstract
43	Pereira et al. 2018	Heterologous adipose derived mesenchymal stem cells and Vitamin D supplementation in patients with recent-onset type 1 diabetes mellitus: Effects on glycemic variability, Joana R. Dantas1	Conference abstract
44	Singh et al. 2017	Long term safety and efficacy of autologous stem	Conference abstract

		cell transplantation for the treatment of type 2 diabetes mellitus	
45	Kapoor et al. 2018	Stem cell transplatation in type 1 diabetes-one year randomised case control study	Conference abstract
46	Feng. 2011	Autologous peripheral blood hematopoietic stem cell transplantation in the treatment of type 1 diabetic mellitus: a report of 16 cases	Conference abstract
47	Li et al. 2018	Effect of autologous bone marrow stem cell transplantation for diabetic nephropathy IV: A multicenter, open, matched intervention trial	Conference abstract
48	Li et al. 2014	Umbilical cord mesenchymal stem cell transplantation for treatment of diabetic lower limb vascular disease	Conference abstract
49	Carlsson et al. 2023	Mesenchymal Stem/Stromal Cells: A single infusion of protransâ® mesenchymal stromal cell product maintains endogenous insulin production in type 1 diabetes patients a long-term follow-up study	Conference abstract
50	Chacon Quevedo et al. 2022	Autologous bone marrow mononuclear cells in the treatment of chronic limb-threatening ischaemia: a proof-of-concept trial	Conference abstract
51	Chen et al. 2016	[The effect of liraglutide in combination with human umbilical cord mesenchymal stem cells treatment on glucose metabolism and Î² cell function in type 2 diabetes mellitus].	Conference abstract
52	Tootee Ali et al. 2015	Application of allotransplantation of fetal liver-derived stem-cells for treatment of Type 1 Diabetes: a single-arm, phase 3 clinical trial	Conference abstract
53	Saltzman et al. 2021	A randomized, double blind, clinical trial to evaluate safety and efficacy of allogeneic mesenchymal human stem cells infusion therapy for endothelial dysfunction in diabetic subjects (ACESO)	Conference abstract
54	Izadi et al. 2020	Mesenchymal Stem Cells Transplantation in newly diagnosed type-1 diabetes patients: a phase I/II Randomized Controlled trial	Conference abstract
55	De Pina Cabral et al. 2019	Allogenic adipose derived mesenchymal stem cells and Vitamin D supplementation in patients with recent-onset type 1 diabetes mellitus: A 3-month follow-up study	Conference abstract
56	Ghodsi et al. 2015	Insulin Independence after Fetal Liver-Derived Cell Suspension Allotransplantation in Patients with Type 1 Diabetes: A Pilot Study	Full text in foreign language, non-translatable
57	Zhang et al. 2011	Promoting Long-Term Survival of Insulin-Producing Cell Grafts That Differentiate from Adipose Tissue-Derived Stem Cells to Cure Type 1 Diabetes	Full text in foreign language, non-translatable
58	Soria-Juan et al. 2021	Efficacy and safety of intramuscular administration of allogeneic adipose tissue derived and expanded mesenchymal stromal cells in diabetic patients	Full text in foreign language, non-translatable

		with critical limb ischemia with no possibility of revascularization: study protocol for a randomized controlled double-blind phase II clinical trial (The NOMA Trial).	
59	Xianliang et al. 2018	Efficacy and safety of autologous bone marrow mesenchymal stem cell transplantation in patients with diabetic retinopathy	No abstract and full text
60	Shuang et al. 2022	Mesenchymal stem cells (MSCs): a novel therapy for type 2 diabetes	No abstract and full text
61	Julio et al. 2019	Hematopoietic stem cell transplantation for treatment of type I diabetes	No abstract and full text
62	Yao et al. 2009	Efficacy and safety of mesenchymal stem cell transplantation in patients with diabetes mellitus	No abstract and full text
63	NCT01068951	Treatment of Patients with Newly Onset of Type 1 Diabetes with Mesenchymal Stem Cells	No abstract and full text
64	NCT03343782	Outcomes of Expanded Autologous Bone Marrow-derived Mesenchymal Stem Cells Therapy in Type II Diabetes	No abstract and full text
65	NCT00690066	PROCHYMALÂ® (Human Adult Stem Cells) for the Treatment of Recently Diagnosed Type 1 Diabetes Mellitus (T1DM)	No abstract and full text
66	NCT01786707	Autologous Stem Cell and Hyperbaric Oxygen Therapy in Type 2 Diabetes Mellitus	No abstract and full text
67	IRCT20171021036903N2	The safety of placental mesenchymal stem cell therapy for the treatment of type 1 diabetes mellitus	No abstract and full text
68	NCT00807651	Autologous Hematopoietic Stem Cell Transplantation for Early Onset Type 1 Diabetes	No abstract and full text
69	Nassar et al. 2015	Effect of cell-free mesenchymal stem cells microvesicles (MVS) and exosomes therapy on Î²-cell mass in type 1 diabetes mellitus (T1DM) | Cochrane Library	No abstract and full text
70	NCT02302599	Mesenchymal Stem Cells to Treat Type II Diabetes	No abstract and full text
71	NCT01413035	Safety and Efficacy Study of Umbilical Cord/Placenta-Derived Mesenchymal Stem Cells to Treat Type 2 Diabetes	No abstract and full text
72	CTRI/2017/12/010878	A clinical study to Evaluate the Safety of stem cells in subjects with Type 1 diabetes	No abstract and full text
73	EUCTR2020-004520-42-SE	Mesenchymal Stromal Cells to prevent further loss of own insulin production in case of illness in Type I Diabetes in children and young adults	No abstract and full text
74	Chen et al. 2012	Effects of acupoint injection of autologous blood on symptoms and plasma motilin and gastrin levels of diabetic gastroparesis patients	No abstract and full text
75	Frogel et al. 2017	Adult stem/progenitor cells derived from peripheral blood as a personalized treatment for critical limb ischemia (CLI)	No abstract and full text

76	Bhansali et al. 2016	Assessment of efficacy of autologous stem cells transplantation by clamp studies in patients with T2DM	No abstract and full text
77	IRCT20210925052566N1	Transplantation of stem cells for the treatment of type 1 diabetes	No abstract and full text
78	Lee et al. 2022	Diabetes duration and obesity matter in autologous mesenchymal stem/stromal cell transplantation in type 2 diabetes patients	No abstract and full text
79	Zhu et al. 2022	The Therapeutic Potential of Mesenchymal Stem Cells in the Treatment of Diabetes Mellitus	No abstract and full text
80	Husakova et al. 2022	Comparison of Three Methods for Preparation of Autologous Cells for Use in Cell Therapy of Chronic Limb-Threatening Ischemia in People with Diabetes	No abstract and full text
81	Shumkov et al. 2022	Long-term Results of Surgical Treatment and Cell Therapy in Patients with Type 2 Diabetes and Chronic Lower Limb Ischemia	No abstract and full text
82	Kim et al. 2018	Bone marrow mesenchymal stem cells as a new therapeutic approach for diabetes mellitus	No abstract and full text
83	Wehbe et al. 2016	Bone marrow derived stem cell therapy for type 2 diabetes mellitus	No abstract and full text
84	Li et al. 2012	Autologous Hematopoietic Stem Cell Transplantation Modulates Immunocompetent Cells and Improves beta-Cell Function in Chinese Patients with New Onset of Type 1 Diabetes	No abstract and full text
85	Packham et al. 2015	Mesenchymal Precursor Cell Therapy for Diabetic Nephropathy: 24 Week Results from a Phase 2A Randomized Controlled Trial	No abstract and full text
86	Zhao et al. 2008	Combined transplantation of autologous peripheral blood and bone narrow stem cells for the treatment of diabetic lower limb ischaemia: Randomized controlled trial	No abstract and full text
87	Giannetti et al. 2007	Randomised, single-blind, controlled clinical study in two parallel groups comparing a treatment with autologous stem cell transplantation (ASCT) and a standard treatment in patients with diabetes mellitus type II	No abstract and full text
88	Arango-Rodríguez et al. 2023	A novel therapeutic management for diabetes patients with chronic limb-threatening ischemia: comparison of autologous bone marrow mononuclear cells versus allogenic Wharton jelly-derived mesenchymal stem cells.	Wrong population in the study (critical limb ischemia)
89	Lian et al. 2023	Safety evaluation of human umbilical cord-mesenchymal stem cells in type 2 diabetes mellitus treatment: A phase 2 clinical trial.	Outcome of interest not included in the study
90	Gibbons et al. 2021	Phase 2a randomized controlled study investigating the safety and efficacy of PDA-002 in diabetic peripheral neuropathy	Outcome of interest not included in the study

91	Zhou et al. 2017	Efficacy, safety and influencing factors of intra-calf muscular injection of bone marrow mononuclear cells in the treatment of type 2 diabetes mellitus-induced lower extremity vascular disease	Stem cell was not cultured or characterized before administration to patients
92	Estrada et al. 2019	Efficacy, safety and influencing factors of intra-calf muscular injection of bone marrow mononuclear cells in the treatment of type 2 diabetes mellitus-induced lower extremity vascular disease	Stem cell was not cultured or characterized before administration to patients
93	Sood et al. 2017	Autologous bone marrow derived stem cell therapy in patients with type 2 diabetes mellitus - defining adequate administration methods	Stem cell was not cultured or characterized before administration to patients
94	Wu et al. 2014	Autologous bone marrow mononuclear cell infusion and hyperbaric oxygen therapy in type 2 diabetes mellitus: an open-label, randomized controlled clinical trial	Stem cell was not cultured or characterized before administration to patients
95	Haller et al. 2013	Autologous Umbilical Cord Blood Infusion followed by Oral Docosahexaenoic Acid and Vitamin D Supplementation for C-Peptide Preservation in Children with Type 1 Diabetes	Stem cell was not cultured or characterized before administration to patients
96	Mohammadzadeh et al. 2013	Therapeutic Outcomes of Transplanting Autologous Granulocyte Colony-stimulating Factor-mobilised Peripheral Mononuclear Cells in Diabetic Patients with Critical Limb Ischaemia	Stem cell was not cultured or characterized before administration to patients
97	Huang et al. 2005	Autologous Transplantation of Granulocyte Colony–Stimulating Factor-Mobilized Peripheral Blood Mononuclear Cells Improves Critical Limb Ischemia in Diabetes	Stem cell was not cultured or characterized before administration to patients

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