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REVIEW

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A meta-analysis on application and prospect of cell therapy in the treatment of diabetes mellitus

Hanluo Li[1], Cheng Chen[1], Yuansheng Wang[1], Wei Yi[1], Peipei Guo[1], Chenguang Yao[1], Jinbiao Liu[1], Yanhong Wei[1], Kanghong Hu[1], Xiaoke Shang[1,2*†] and Sini Kang[1*†]

Abstract

Objective Diabetes mellitus (DM) is a grave autoimmune disorder because of no insulin self-generation. Currently, mainly clinical methods exist, serious adverse effects leading to stem cell therapy are considered. The mesenchymal stem cells (MSCs), require high differentiation capacity and are judged as crucial in DM treatment. The meta-analysis aimed to systemically analyze the particular types of MSCs which play a more important role in DM and which DM is treated more effectively.

Method A systematic review was conducted on the published literature, clinical trials and observational studies, utilizing databases such as PubMed, Embase, Cochrane and clinicaltrial.gov. RevMan software was adopted to draw Forest Plot and Funnel Plot, and subgroup analysis were employed to evaluate heterogeneity between different groups.

Results We identified the meta-analyses of 34 unique random controlled trials and divided our own systematic reviews into 8 groups. The MSCs were associated with placebo (OR = 2.79, 95% CI [1.63, 4.75]), Standard Clinical Treatment (SCT) (OR = 4.12, 95% CI [2.76, 6.14]), and monocyte (OR = 6.52, 95% CI [3.56, 9.48]). The comparison between Autologous MSCs and Allogenic MSCs (OR = 4.64, 95% CI [3.42, 6.31]), Autologous BMMSCs and other MSCs (OR = 5.28, 95% CI [3.64, 7.66]), Allogenic ASCs and UCMSCs (OR = 3.54, 95% CI [1.83, 6.86]), Type I DM and Type II DM (OR = 3.10, 95% CI [1.79, 5.38]), intravenous injection and other injections (OR = 4.81, 95% CI [3.34, 6.94]), diabetic foot ulcers and diabetic neurological disease (OR = 3.88,,95% CI [2.53,5.95]).

Conclusion Current evidence suggests that MSCs hold significant potential for treating DM, demonstrating considerably high safety and efficacy. MSCs exhibit higher therapeutic benefits compared to monocytes, with autologous MSCs offering better clinical outcomes than allogenic sources. MSCs (BMMSCs) proved more effective than other types of MSCs. However, no significant differences were observed between adipose-derived MSCs (ASCs)

†Xiaoke Shang and Sini Kang authors contributed equally to this work.

*Correspondence:
Xiaoke Shang
shangxiaoke@hbut.edu.cn
Sini Kang
kangsini@hbut.edu.cn

Full list of author information is available at the end of the article

and umbilical cord-derived MSCs (UCMSCs) in the allogeneic setting. Moreover, MSCs show more pronounced therapeutic effects in Type II DM, and the difference among the injection methods is minimally observed. In conclusion, the research scope on DM is relatively limited in this study and further research is necessary to improve the reliability of the estimates.

Keywords MSCs, Autologous MSCs, Allogenic MSCs, Type I DM, Type II DM, Exosomes, iPSC

Introduction

Diabetes mellitus (DM) is a rapidly increasing chronic immunometabolism disorder and tends to occur in all ages [1].It is classified into Type I DM and Type II DM, both of which share similar symptoms such as thirst, blurred retina, and increased urine [2], resulting from serious complications such as hyperglycemia, polyuria, diabetic wounds and retinal damage [3], which significantly impact public health. In 2021, over 540 million people worldwide are suffering from DM, with the predicted number of patients over 640 million by 2031 [4]. The underlying mechanisms of Type I and Type II DM are different. Type I DM is an autoimmune disease characterized that β cells are attacked by the immune system, leading to insufficient insulin production and hyperglycemia and emaciation [5]. In contrast, Type II DM is due to insulin resistance, which impairs glucose transportation into cells in the presence of high level of insulin [6]. This condition is the most prevalent form of diabetes, detrimentally affecting adolescents and individuals with obesity in a significant portion of the population [7]. It is considered the disorder of glucose regulation and the cause of significant damage to multiple organs and systems [8].

While the pathogenesis of DM is complex and multifactorial, several common mechanisms have been identified. Firstly, hyperglycemia damages pancreatic function by preventing it from producing insulin to counteract the elevated blood glucose levels [9]. Secondly, hyperglycemia can induce DNA damage in pancreatic cells, thereby increasing the risk of pancreatic cancer. Furthermore, inflammatory factors such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) are identified to activate mitochondria that trigger autophagy, leading to an increase in reactive oxygen species (ROS) and elevated blood glucose [10]. It's evident that there is a well-established correlation between adipocyte function and inflammatory factors, which oxidative stress and mitochondrial dysfunction are key contributors to inflammation [11]. Lastly, unsaturated fatty acids stimulate the eukaryotic initiation factor (eIF) through the cell membrane, promoting phosphorylation and accelerating the synthesis of saturated fatty acids.

The current clinical drugs are mainly oral drugs and islet injections [12]. Metformin, a kind of routine oral hypoglycemic medicine, has the cognitive for prohibit ND3 circle in biological oxidation reactions and intercept glycolysis. It presents the benefits of enhancing the utilization about peripheral tissues absorbing glucose and declining the hypertension and lipids. However, it also causes adverse effects seriously such as nausea, vomiting, bloating, and diarrhea et al. [13] The cell treatment strategy, leveraging cell high capacity for differentiation to induce insulin, is another effective method to treat DM [14]. Nevertheless, an important limitation of this approach is the extent to which they are often serious [15]. The main stem cell including embryonic stem cells, microglia and vascular cells [16], but they inhibit Notch Pathway to differentiate into βcell or MAPK/ERK signaling to regenerate cells resulting an ideal approach of cell treatment strategy needs to be applied urgently [17].

Given the current limitations of conventional treatments for DM, it is urgent to explore alternative therapeutic solutions with high efficiency and safety. Mesenchymal stem cells (MSCs) exhibit promising outcomes compared to traditional treatments such as metformin in the treatment of DM. Since initially discovered in the bone marrow in early 90s, mesoderm-derived multipotent MSCs aroused the extensive attention due to their ability of self-renew and differentiation into a variety of cell types, such as chondrocytes [18], adipocytes [19], osteoblasts [20], and other cell types with little tumorigenicity and tumorigenicity [21], which are crucial to tissue repair and regeneration without ethical issues. In addition to their regenerative capabilities, MSCs presents immunomodulatory [22] and anti-inflammatory [23] effects to promote cell proliferation, antioxidants [24], and anti-fibrosis [25]. These findings expand our understanding of MSCs and provide a promising strategy for DM treatment. However, many challenges such as standardization and large-scale production of MSC sources still remain, and research and application on MSCs are in development, which provide a brand-new expectation for their clinical treatment [26].

To systemically evaluate the clinical efficiency of MSCs therapy for treating DM, this research utilizes meta-analysis to comprehensively determine whether and which MSCs are effective compared with several therapy using other types of cells, enabling more reliable and comprehensive conclusions. The volume of clinical data and credibility of statistical analysis are sourced from clinical databases such as PubMed, Embase, Cochrane, and Clinicaltrials.gov. This meta-analysis evaluates the safety and efficacy of MSC treatments, and also analyzes critical

parameters such as the patient age, medical history, and treatment regimen. This study provides comprehensive understanding of MSC therapies, facilitating more informed decisions in clinical practice.

The method and tool of meta-analysis

Subject words and free words

The computerized bibliographic databases Clinicaltrial.gov PubMed, EMBASE, and Cochrane library were screened for clinical trials from inception to July 2024, The main search terms used were (Diabetes Mellitus Noninsulin-Dependent or Diabetes Mellitus Ketosis Resistant or Diabetes Mellitus Non-Insulin Dependent or Diabetes Mellitus Stable or NIDDM or Diabetes Mellitus Noninsulin Dependent or MODY or Diabetes Mellitus Slow Onset or Type 2 Diabetes Mellitus or Noninsulin Dependent Diabetes Mellitus or Diabetes Maturity-Onset or Type 2 Diabetes or Diabetes Mellitus Adult-Onset), and (Lipoatrophic Diabetes Mellitus or Lipoatrophic Diabetes or Diabetes Lipoatrophic or Diabetes Lipoatrophic or Lipoatrophic Diabetes or Diabetes Mellitus). 1991 articles in PubMed,133 articles in Cochrane, and 3392 articles in Embase were collected in a total of 5416 articles. The literature was screened against a range of exclusion criteria, such as non-clinical trials and review articles, resulting in 35 entries. In addition, a total of 83 results were found from Clinicaltrial.gov and key factors were collated and summarized such as the start time, end time, number of trials, age, and experimental results of these clinical trials (Table 1).

Parameter setting of Revman manager 5.4 software

The latest version of Revman Manager 5.4 software has been utilized to organize the search process to produce a clear and visible graph and flowchart and randomization and blinding experiments were employed to risk assessment. 34 cases about the number, age, and country of participants are sorted and comparative to elucidate their features. MSCs are compared with the placebo, Standard Clinical Treatment, and monocyte and Autologous MSCs and Allogenic MSCs are also compared to judge which is better.

Inclusion and exclusion criteria

Inclusion Criteria (1): Prospective experiments, including RCTs (randomized controlled trials) (2) Journal, articles, and abstracts written in English (3) Participants diagnosed with DM or complications (4) During the experiment, the number of participants cannot less than 10 people even if the participants drop out in the midway (5) The length time of treatment cannot be less than 1 year (6) the level of HA1c, C-peptide or TcPO2 should be a significant reference during the treatment of DM (7): MSCs sources used in the study include bone marrow, adipose tissue, or other reliable sources. (8): The study provided sufficient data to evaluate the effectiveness and safety of MSCs in the treatment of DM, such as the degree of improvement in blood glucose level, improvement in insulin sensitivity, improvement in insulin secretion function, etc. Exclusion Criteria: (1) retrospective or observational studies; (2) non-English literature or unpublished research; (3) the sample size is too small to produce reliable results; (4) The treatment time is less than 1 year, or no clear treatment time is provided; (5) insufficient data are provided for validity and safety assessment; (6) studies of low quality or inability to obtain complete data.

Results

Basic information about the included studies, including study design, sample size, and patient characteristics

Flow diagram

A comprehensive literature search yielded 1991 articles on PubMed and a total of 3425 articles on Embase and Cochrane databases, with 1159 duplicates found. After exclusion criteria applied, a total of 4129 articles were excluded for the following reasons: (1) 2530 articles were non-clinical studies, such as basic research, animal experiments; (2) 858 articles were review articles, which were not applicable for meta-analysis; (3) 741 articles were deemed irrelevant to the research topic after reading the abstracts; (4) 65 articles were excluded due to lack of relevance after reading the full text; (5)28 articles did not meet the experimental design requirements for randomized controlled trials (RCTs). Through this screening process, 35 studies were selected for meta-analysis [27–60]. (Fig. 1).

The data from 34 MSC-based treatments for DM were collected and summarized in a table (Table 2). This table provides a clear overview of these studies for a clear comparison on the study characteristics and experimental designs. By collating and analyzing this information, the reliability and applicability of these studies were understood and evaluated, thereby providing more valuable foundation to support the meta-analysis.

Risk assessment

The risks of the included studies were assessed throughout the research progress, determining primarily whether the included articles provided a clear randomized, blind, and authentic experimental protocol. Experimental procedures, groups and results of randomized experiments were well-documented and categorized in the contexts, indicating the credibility of the studies. However, nearly half of studies informed consent from participants about the clinical trial, yet the specific content of the communications remained non-disclosed. Therefore, the risks of performance bias (Blinding of participants and

Table 1 The information of clinicaltrials.gov about different types of MSCs (MSC) treat DM mellitus

ID	Disease	Age	Type of cell	Num	Interventions	Efficacy
NCT02940418	Type 1 DM	18–35	Allo ASCs	20	injected	efficacy
NCT02893306	Type 1 DM	18 or older,	Allo BMSCs	10	IV	efficacy
NCT05595681	Foot ulcers	40–75	Allo ASCs	30	/	efficacy
NCT04466007	Limb Ischemia	40–90	Allo ASCs	90	IV	unknow
NCT04869761	Chronic Kidney	30–80	Allo ASCs	40	intravenous	no AE
NCT02384018	Type 1 DM	more than 18	Auto BMSCs	3	portal vein	efficacy
NCT03920397	Type 1 DM	16–35	Allo ASCs	30	Infusion	efficacy
NCT03840343	Type 2 DM	45–75	Auto ASCs	2	IA	efficacy
NCT03259217	Foot ulcers	/	Auto ASCs	40	/	50% efficacy
NCT01257776	Limb Ischemia	18–85	Auto ASCs	33	IA	no AE
NCT05308836	Type 1 DM	/	Auto ASCs	10	IV	unknow
NCT02831075	Foot ulcers	18–80	Allo ASCs	240	reinfection	efficacy
NCT03865394	Foot ulcers	more than 18	Allo ASCs	46	cover fibrin gel	efficacy
NCT03183726	Foot ulcers	18–80	Allo ASCs	4	/	unknow
NCT02387749	Neuropathy	18–45	Auto BMSCs	10	/	efficacy
NCT01142050	Type 2 DM	18–75	Auto BMSCs	24	intravenously	efficacy
NCT03754465	Foot ulcers	18–80	Allo ASCs	56	/	efficacy
NCT04497805	Foot ulcers	18–80	Allo ASCs	64	/	efficacy
NCT01686139	Foot ulcers	18–81	Allogeneic BMSCs	12	injected	no AE
NCT02796079	Type 1/2 DM	18–80	Auto BMSCs	240	injected	efficacy
NCT03370874	Foot ulcers	18–75	Allo ASCs	150	/	efficacy
NCT03343782	Type 2 DM	more than 18	Auto BMSCs	30	intravenously	efficacy
NCT03509870	Foot ulcers	18–80	Allogeneic BMSCs	2	/	no AE
NCT01759823	Type 2 DM	30–70	Auto BMSCs	30	injected	efficacy
NCT02585622	Type 2 DM	40–85	Allogeneic BMSCs	48	intravenously	no AE
NCT03751735	ED	25–70	Allo UCMSCs	9	injected	efficacy
NCT02945449	ED	25–70	Allo UCMSCs	9	injected	efficacy
NCT03288571	Nephropathy	35–70	Allo UCMSCs	20	injected	efficacy
NCT03361631	Type 1 DM	18–50	Auto BMSCs	13	ICI	efficacy
NCT04569409	Foot ulcers	19–75	Allo ASCs	104	/	efficacy
NCT04078308	Type 1 DM	8–40	Auto BMSCs	20	IV	no AE
NCT03276312	Foot ulcers	more than 18	Auto ASCs	112	injected	efficacy
NCT03973827	Type 1 DM	18–41	Allo UCMSCs	15	infusion	efficacy
NCT01068951	Type 1 DM	18–40	Auto BMSCs	20	intravenously	efficacy
NCT01065337	Limb Ischemia	18–80	Auto BMSCs	30	injections	efficacy
NCT01143168	Type 1 DM	18–50	Auto BMSCs	24	intravenously	no AE
NCT04125329	Nephropathy	18–60	Allo UCMSCs	15	injection	no AE
NCT01157403	Type 1 DM	10–40	Auto BMSCs	80	intravenously	efficacy
NCT01219465	Type 1 DM	3–35	Allo UCMSCs	50	intravenously	efficacy
NCT03325322	Chronic Kidney	40–80	Allo ASCs	30	/	efficacy
NCT04441658	Type 2 DM	30–75	Allo UCMSCs	30	intravenously	efficacy
NCT04216849	Nephropathy	30–70	Allo UCMSCs	54	intravenously	unknow
NCT03943940	Type 2 DM	18–70	Auto BMMNCs and Allo UCMSCs	60	intravenous	unknow
NCT04501341	Type 2 DM	30–60	Auto BMSCs	15	blood vessels	efficacy
NCT02886884	ED	21–90	Allo ASCs	16	IV	no AE
NCT03484741	Type 1 DM	18–45	Auto BMSCs	15	IV	efficacy
NCT02304588	Foot ulcers	30–78	Auto BMSCs	20	injected	efficacy
NCT05783115	Foot ulcers	35–80	Auto BMSCs	46	/	efficacy
NCT01322789	Type 1 DM	12–35	Auto BMSCs	10	IV	efficacy
NCT01374854	Type 1 DM	18–40	Allo UCMSCs	44	infused	efficacy
NCT04776239	ED	more than 18	Allo BMSCs	30	IV	efficacy
NCT01719640	Type 2 DM	40–65	Auto BMSCs	22	infusion	efficacy
NCT02057211	Type 1 DM	18–40	Auto BMSCs	10	/	efficacy

Table 1 (continued)

ID	Disease	Age	Type of cell	Num	Interventions	Efficacy
NCT02763423	Type 1 DM	12–35	Allo UCMSCs	30	IV	efficacy
NCT00646724	Type 1 DM	18–60	Allo UCMSCs	30	cotransplantation	efficacy
NCT02834858	VC	18–80	Allo UCMSCs	240	injection	efficacy
NCT04562025	Nephropathy	30–65	Auto UCMSCs and Allo UCMSCs	38	intravenously	no AE
NCT04972890	ED	18–65	Allo UCMSCs	12	injection	efficacy
NCT02579148	Type 1/2 DM	20–65	Allo UCMSCs	/	ICI	efficacy
NCT00955669	Limb Ischemia	40–70	Auto BMSCs	40	IM	unknow
NCT05061030	Type 1 DM	7–21	Allo UCMSCs	66	intravenously	efficacy
NCT01216865	Foot ulcers	18–75	Allo UCMSCs	50	Muscular injection	unknow
NCT03406585	Type 1 DM	18–40	Allo UCMSCs	24	infusion	efficacy
NCT04061746	Type 1 DM	18–30	Allo UCMSCs	60	IV	efficacy
NCT02302599	Type 2 DM	20–65	Allo UCMSCs	103	Infusion	efficacy
NCT02619877	Foot ulcers	18–80	Allo ASCs	59	/	no AE
NCT03183804	Foot ulcers	18–80	Allo ASCs	54	/	no AE
NCT03248466	Foot ulcers	20–70	Auto BMSCs	60	/	efficacy
NCT05507697	Neuropathy	18–55	Allo UCMSCs	42	injection	efficacy
NCT03912480	Type 1 DM	25–70	Auto BMSCs	24	Injection	efficacy
NCT00690066	Type 1 DM	12–35	Allo ASCs	63	IV	unknow
NCT01954147	Type 2 DM	35–65	Allo UCMSCs	100	/	unknow
NCT04464213	Foot ulcers	18–75	Auto PMSCs	43	/	efficacy
NCT05003908	Type 1/2 DM	/	Auto PMSCs	20	IV	efficacy
NCT01496339	Type 1 DM	18–75	Auto BMSCs	50	IV	unknow
NCT02286128	Type 2 DM	more than 18	Auto BMSCs	2	/	efficacy
NCT01413035	Type 2 DM	18–80	Allo UCMSCs and Auto PMSCs	30	/	efficacy
NCT04104451	Foot ulcers	more than 18	Allo UCMSCs	16	/	efficacy
NCT02943486	Foot ulcers	40–80	Auto BMSCs	51	Intradermic	efficacy
NCT02745808	Type 1/2 DM	20–65	Allo UCMSCs	30	ICI	efficacy
NCT02138331	Type 1 DM	18–60	Allo UCBMSCs	20	IV	efficacy
NCT04642911	Type 2 DM	/	Auto BMSCs	91	/	efficacy
NCT02672280	Foot ulcers	18–70	Allo UCBMSCs	30	/	no AE

personnel) and detection bias (Blinding of outcome assessment) were mainly classified as uncertain and even high. Despite these concerns regarding the blinding methods, the overall reliability of the included studies was elucidated acceptable (Fig. 2). It is important to notice that these bias factors potentially influenced the efficacy validity and safety assessments. Nonetheless, such thorough risk assessment in this study improved the authenticity of the findings and conclusions of the meta-analysis, providing more efficient treatment options for the physicians and patients.

Dichotomous and continuous variables

Placebo

In order to evaluate the safety and adverse effects of MSCs during treatment, a meta-analysis of fourteen studies was performed in this study. The data were dichotomous, and analysed using a fixed effect model with odds ratio as the effect measure. Individual confidence intervals and total confidence intervals were set at 95%. The experiment group was placed on the right side of the forest plot, while the control group was on the left. The index is designed to explore the incidence of adverse effects with the results visualized through Forest plot and Funnel plot.

Fourteen studies were involved in this meta-analysis. As shown in Fig. 3ab, safety of MSCs was assessed compared to placebo and no treatment control for DM (OR = 2.79, 95% CI [1.63, 4.75], $P = 0.0002$). Generally, the point of inclusion study deviated toward the right and was identified for benefiting the experimental group. Thus, it was a significant benefit for MSCs (OR = 2.79), indicating they were a safer therapeutic option. Meanwhile, the confidence interval (95% CI) did not intersect the null value (OR = 1). Hence, both forest and funnel plot results suggests that MSCs can be safer compared to placebo in clinical trials for DM(Fig. 3ab).

Standard clinical treatment SCT

Standard clinical treatments for DM are typically insulin injection or oral hypoglycemic agents, combined with dietary and exercise intervention. In this meta-analysis, the therapeutic efficacy of MSCs was examined compared to standard clinical treatment (SCT). A total of 18

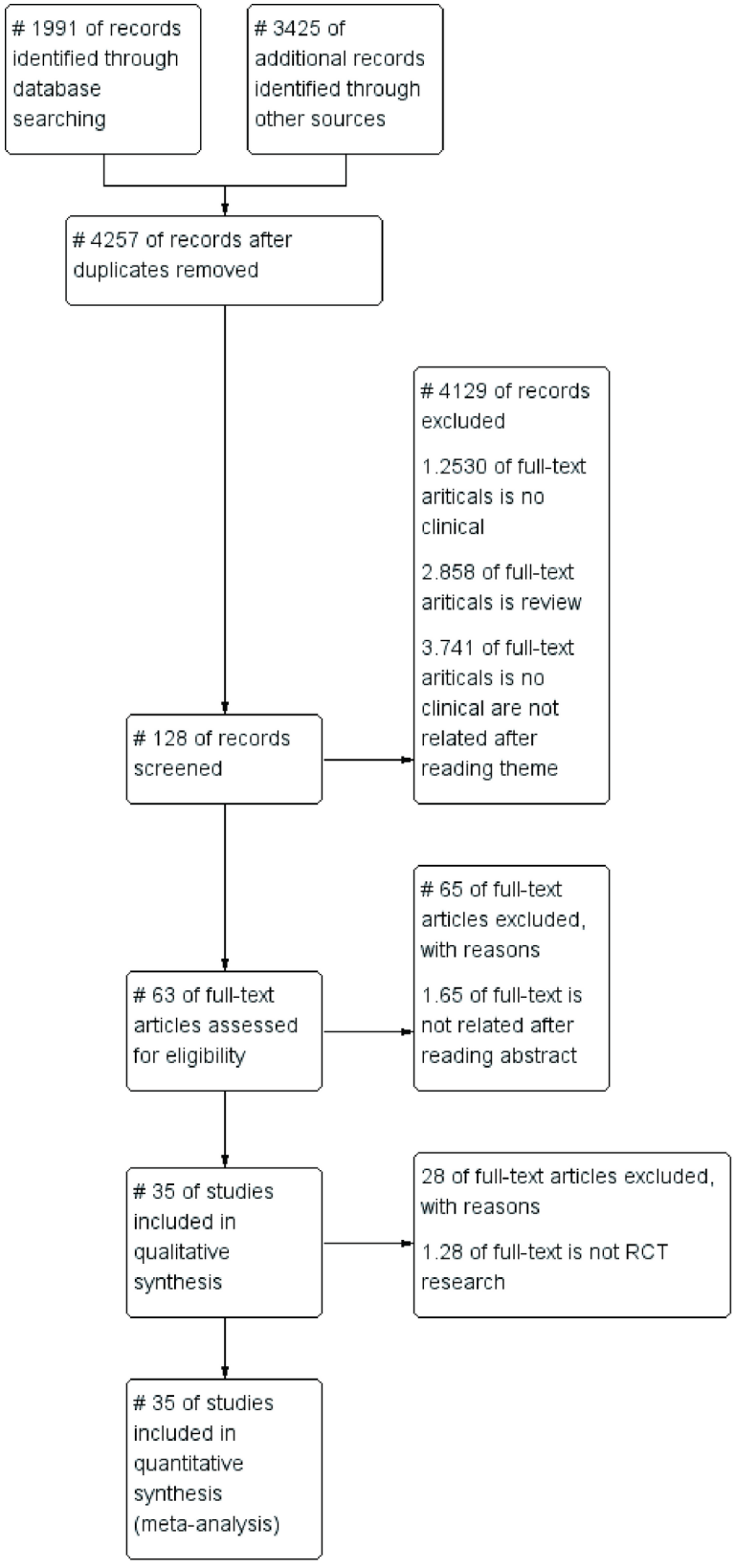


Fig. 1 Flow diagram of the meta-analysis study selection process

Table 2 Information from 34 studies on the treatment of DM mellitus adopting MSCs from pubmed、embase and Cochrane."/" represents no data

Author	Date	Type Of Cell	Routes	Num (M/F)	Age
Araujo	2020	Allo ASCs	injection	13(7/6)	16–35
Dantas, J. R.	2021	Allo ASCs	vessel injection	13(6/7)	16–35
Moon	2019	Allo ASCs	/	39(27/12)	26–80
Uzun, E.	2021	Allo ASCs	injection	20(12/8)	51–64
Jay	2015	Allo BMSCs	injection	31(21/10)	44–66
Packham	2016	Allo BMSCs	/	20(15/5)	54–83
Perico, N.	2023	Allo BMSCs	injection	16(16/0)	54–73
Skyler, J. S.	2015	Allo BMSCs	injection	31(21/10)	44–66
Cai, J.	2016	Allo UCMSC	vessel injection	42(20/22)	18–40
Chen, P.	2016	Allo UCMSC	artery injection	12(12/0)	55–65
Lian, X. F.	2023	Allo UCMSC	inoculate	34(28/6)	44–58
Arango	2023	Allo UCMSC	vessel injection	24(17/7)	51–85
Lu, J.	2021	Allo UCMSC	IV	53(25/28)	10–41
Wu, Z.	2022	Allo UCMSC	Catheter injection	42(28/14)	26–47
Hu, J.	2013	Allo UCMSC	injection	29(17/12)	8–24
Hu, J.	2016	Allo UCMSC	injection	61(33/28)	45–61
Lonard	2019	Auto ASCs	injection	114(86/28)	57–82
Dash, N. R.	2009	Auto BMSCs	injection	/	/
Gu, X.	2018	Auto BMSCs	IVI	17(11/6)	45–67
Lu, D.	2011	Auto BMSCs	injection	37(15/22)	55–75
Lu, D.	2019	Auto BMSCs	injection	47(30/17)	40–70
Bhansali, A.	2014	Auto BMSCs	vein injection	21(16/5)	46–56
Bhansali, S.	2017	Auto BMSCs	TFI	/	/
Carlsson	2015	Auto BMSCs	injection	18(13/5)	22–29
Giannopoulou, E. Z.	2014	Auto BMSCs	injection	17(9/8)	2–11
Gibbons,	2021	Auto BMSCs	IM	16(7/9)	65–75
Izadi, M.	2022	Auto BMSCs	injection	21(11/10)	8–23
Mirzaei, M.	2021	Auto BMSCs	intracavernosal	/	57–71
Mohammadzadeh	2017	Auto BMSCs	injection	/	55–72
Wang, H.	2018	Auto BMSCs	PVI	104	26–46
Meamar, R.	2021	Auto PMSCs	/	18(15/3)	46–76
Carlsson	2023	Auto UCMSC	injection	23(17/6)	18–40
Haller, M. J.	2013	Auto UCMSC	/	/	/
Qin, H. L.	2016	Auto UCMSC	injection	53(32/21)	68–78

studies were included for analysis. The parameters are listed as follows: The data was dichotomous, using a fixed effect model and odds ratio as the effect measure, with 95% confidence intervals.

Seventeen studies were involved to assess effectiveness of MSCs versus SCT for DM in this meta-analysis. The pooled odds ratio (OR = 4.12, 95% CI [2.76, 6.14], $P < 0.0001$) indicated a significant therapeutic benefit of MSCs over SCT (Fig. 4ab). The OR significantly exceeds 1, which suggested MSCs' superiority as a treatment option. The confidence intervals did not intersect the null value (OR = 1). The results presented heterogeneity ($P = 0.0002$), and their reliability was conformed (I^2=0%). Overall, MSCs can be considered as a more effective therapeutic strategy compared to SCT in clinical trials for DM(Fig. 4ab).

Monocytes

Previous studies have reported that monocytes also have a certain therapeutic effect on DM. To evaluate the therapeutic effects of MSCs versus monocytes in DM treatments, five studies were collected, and their transcutaneous oxygen pressure (TcPO2) was analyzed as it is the only consistent factor across the studies. The subjects of the study were divided into experimental (MSCs) and control (monocytes) groups. A continuous variable method was utilized, with a fixed-effect model and mean difference as the effect measure. The individual confidence intervals and the total confidence intervals were set at 95%. The experiment group was placed on the right and the control group on the left in the forest plot.

The mean difference (MD = 6.52, 95% CI [3.56, 9.48], $P < 0.0001$) indicated that MSCs were a more effective therapeutic regimen when compared to monocytes. The

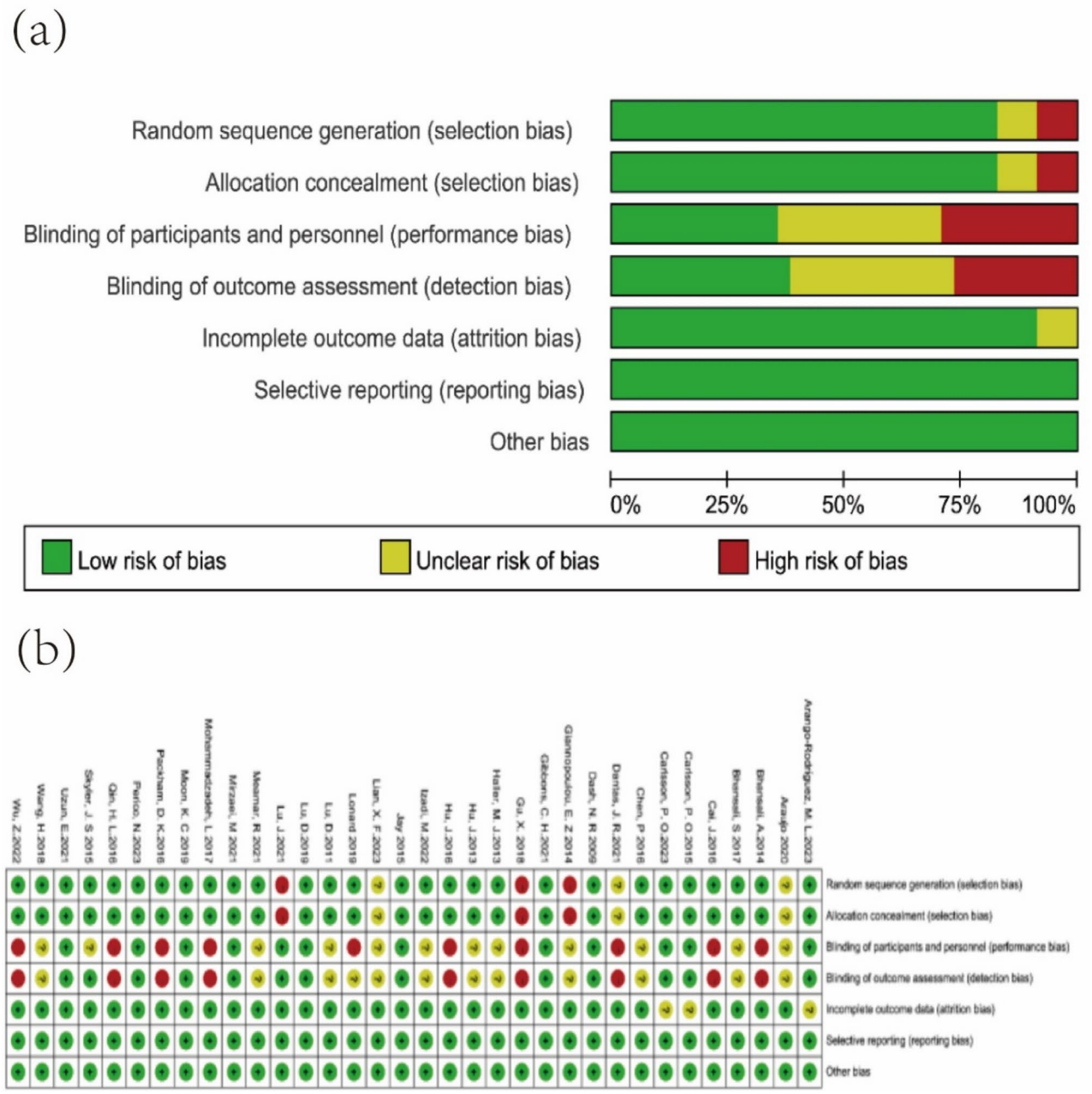
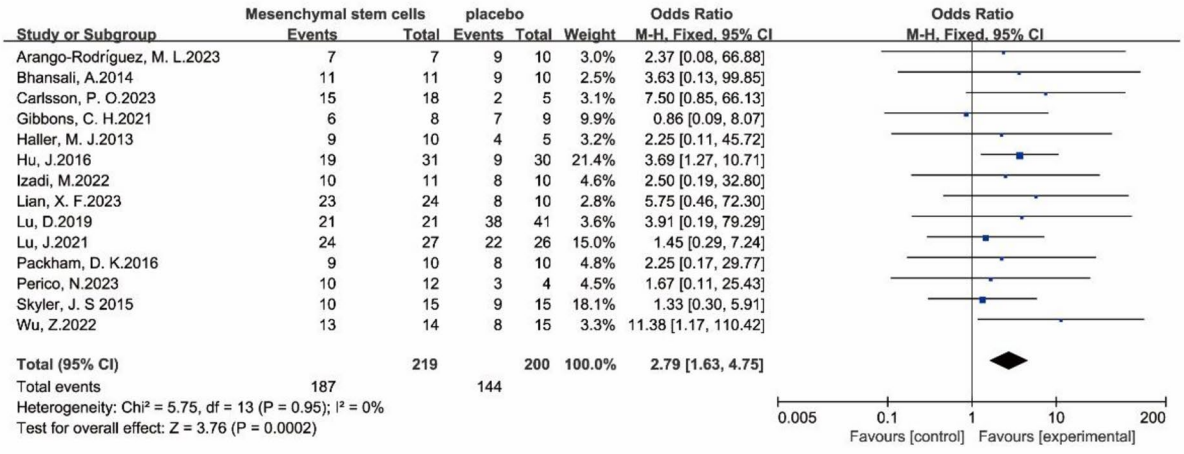


Fig. 2 The graph of risk assessment. risk of bias graph about the meta-analysis of DM mellitus treated with MSCs. B) Risk of bias summary about the meta-analysis of DM mellitus treated with MSCs

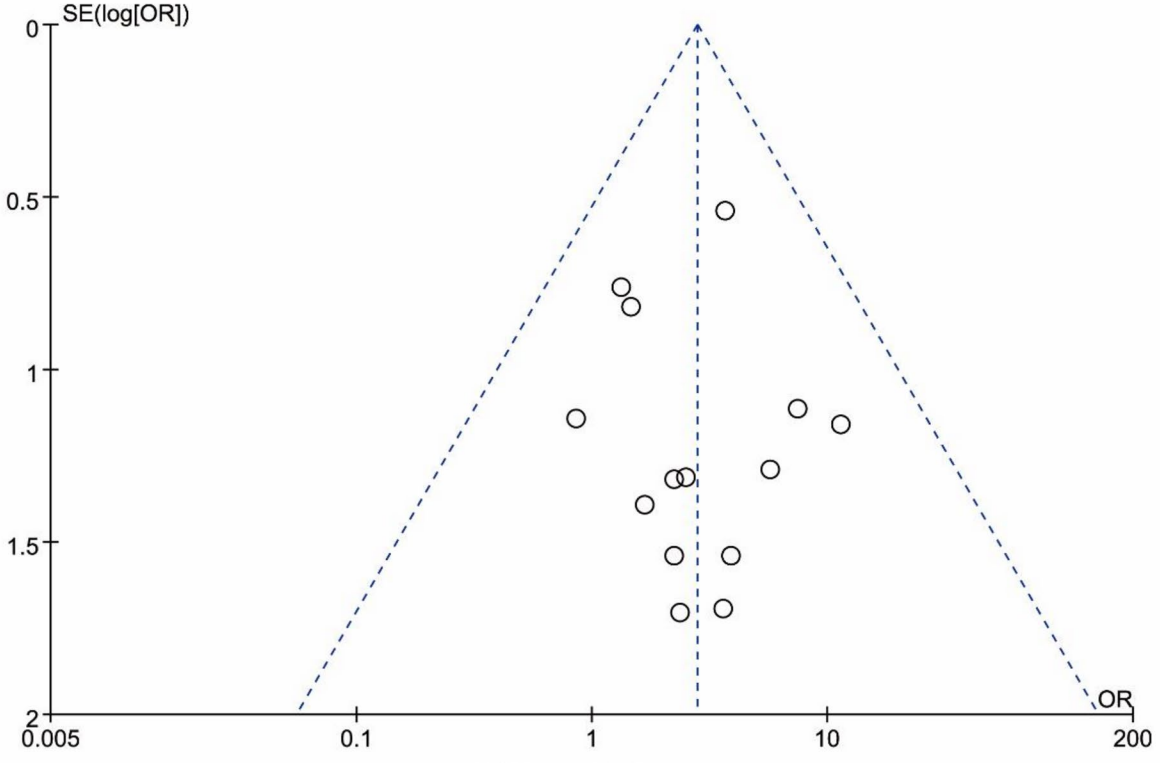
95% confidence interval did not intersect the null value (OR = 1). Mild heterogeneity was present (I^2=33%). Due to the limited data, it is necessary to conduct further studies to clarify the complexities observed in this analysis (Fig. 5ab).

The comparison of autologous and allogeneic

Autologous cells, derived from the patient's own body, can prevent immune rejection, whereas allogeneic cells, derived from other individuals, can offer broader applications. After ensuring the MSCs are superior to other approaches, this meta-analysis categorizes the cells into autologous and allogeneic groups to assess their efficacy. The data was dichotomous using a fixed-effect model and mean difference as the effect measure. The individual confidence intervals and the total confidence intervals were set at 95%. The experiment groups (Autologous and Allogeneic cells) were placed on the right and the control group was on the left in the forest plot.



(a)Forest Plot



(b)Funnel Plot

Fig. 3 (**a**) stands for Forest plot. The forest plots of the included studies compare MSCs versus placebo/no treatment control for treating DM mellitus. (**b**) stand for the Funnel plot. The funnel plot of the included studies comparing MSCs versus placebo/no treatment control for treating DM mellitus

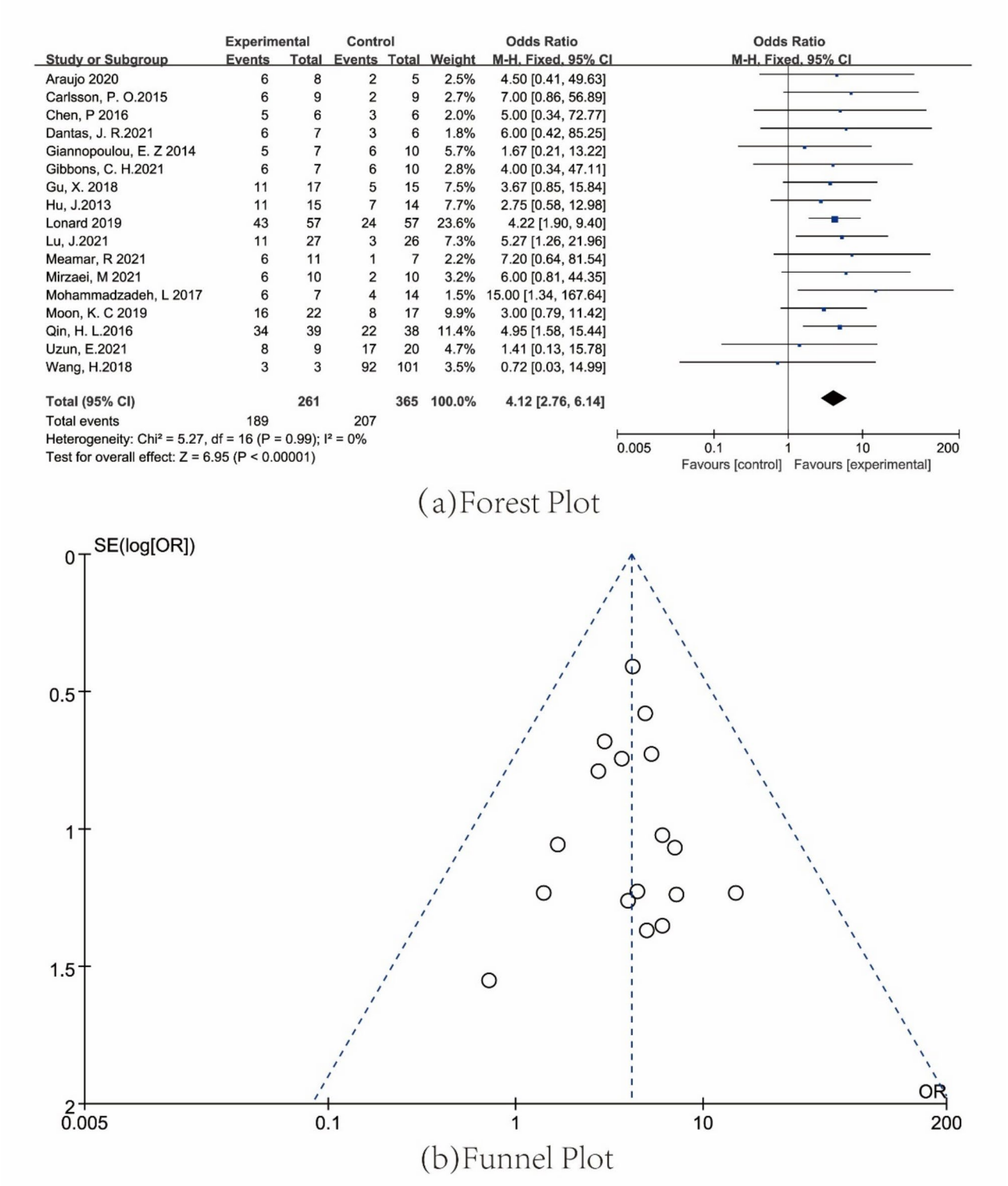


Fig. 4 (**a**) stands for Forest plot. The forest plots of the included studies compare MSCs (MSC) versus standard clinical treatments SCT for treating DM mellitus. (**b**) stand for the Funnel plot. The funnel plot of the included studies comparing MSCs (MSC) versus standard clinical treatments SCT for treating DM mellitus

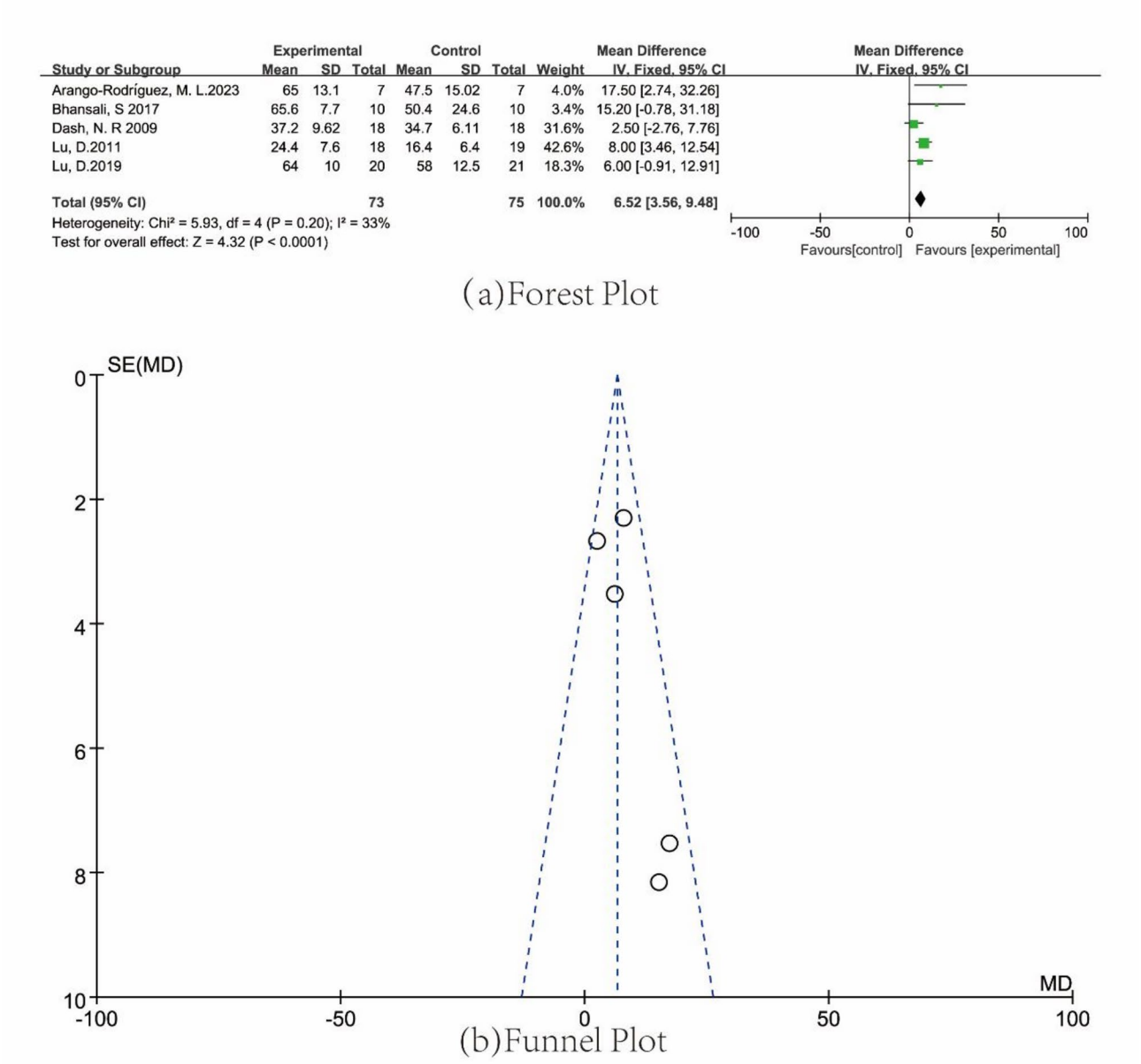


Fig. 5 (**a**) Forest plots. The forest plots of the included studies comparing MSCs (MSC) versus monocytes for treating DM mellitus. (**b**) Funnel plot. The funnel plot of the included studies comparing MSCs (MSC) versus monocytes for treating DM mellitus

A meta-analysis of 13 autologous and 9 allogeneic studies revealed significant differences between the two cell types for treating diabetes mellitus (OR = 4.64, 95% CI [3.42, 6.31], $P < 0.0001$). The results indicate that autologous cells are more effective than allogeneic cells, with a higher combined effect size (5.28 [3.64, 7.66] vs. 3.52 [2.04, 6.06]). The 95% confidence interval does not intersect the null value (OR = 1), and the heterogeneity was low (I^2=3.0%). These findings support autologous MSCs as a superior therapeutic approach compared to allogeneic MSCs in DM treatment (Fig. 6ab).

The comparison of internal autologous

Autologous stem cells can be sourced from bone marrow, umbilical cord, adipose, and placenta. After ensuring the superior efficacy of the autologous MSCs over allogeneic MSCs, a further analysis was conducted by dividing into two major categories of BMMSCs and the other MSCs. The parameters are listed as follows: The data type is dichotomous, the analysis model employed is a fixed effect model, and the effect measure utilized is the odd ratio. the individual confidence intervals and the total confidence intervals are set at 95%. The experiment group ——BMMSCs and the other MSCs were placed on

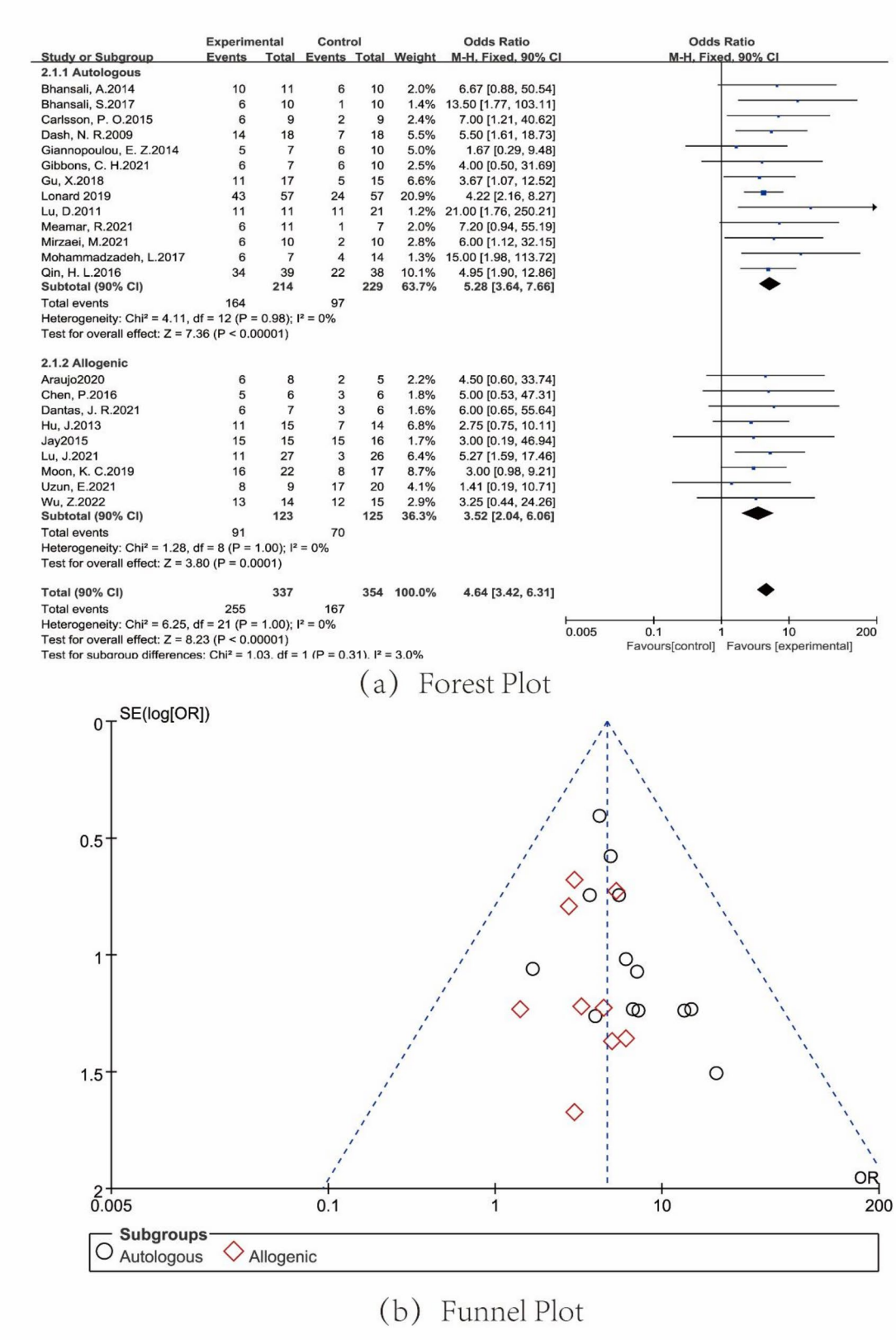


Fig. 6 (**a**) stands for Forest plot. The forest plots of the included studies compare Autologous versus Allogeneic for treating DM mellitus. (**b**) stand for the Funnel plot. The funnel plot of the included studies comparing autologous versus allogeneic for treating DM mellitus

the right and the control group was on the left in the forest plot.

Among the 13 autologous MSC studies, 9 were focused on BMMSCs and 4 studies were other MSCs. Results showed significant differences between BMMSCs and the other MSCs for treating DM (OR = 5.28, 95% CI [3.64, 7.66], $P < 0.0001$). BMMSCs are more effective (OR = 5.28) than other MSCs. The results were reliable (I^2=8.6%). Subgroup analysis further showed BMMSCs had a combined effect size of 6.82, outperforming other MSCs (effect size: 4.23), making BMMSCs a more crucial treatment for DM (Fig. 7ab).

The comparison of internal allogenic

Although allogeneic MSCs are generally less effective than autologous MSCs, they remain a vital therapeutic option, and their efficacy varies across types. To explore these complexities, the allogeneic cells were divided into two major categories: ASCs and UCMSCs. The parameters are listed as follows: The data type is dichotomous, the analysis model employed is a fixed effect model, and the effect measure utilized is the odd ratio. The individual confidence intervals and the total confidence intervals are set at 95%. The experiment group ——ASCs and UCMSCs were placed on the right and the control group was on the left in the forest plot.

Among the 8 studies on allogenic MSCs, the cells were classified into two groups: ASCs and UCMSCs. Data from 4 ASC studies and 4 UCMSC studies revealed a significant treatment effect for both groups in DM (OR = 3.54, 95% CI [1.83, 6.86], $P = 0.0002$). Both ASCs and UCMSCs presented strong curative effects (OR = 3.54). 95% CI in the meantime is [1.83, 6.86] which does not intersect the invalid line OR = 1. (Fig. 8a). An in-depth study reveals the combined effect size of ASCs is 3.09 [1.16, 8.24], and meanwhile, UCMSCs are 2.25 [1.10, 4.58] showing no significant difference. Thus, no significant difference was observed between ASCs and UCMSCs.

The comparison of type I and type II DM

MSCs have demonstrated therapeutic potential in treating many DM complications Type I and Type II DM. The parameters are listed as follows: The data type is dichotomous, the analysis model employed is a fixed effect model, and the effect measure utilized is the odd ratio. The individual confidence intervals and the total confidence intervals are set at 95%. The experiment groups (type I and type II DM) were placed on the right and the control group was on the left in the forest plot.

Twelve studies were grouped into categories of type I and type II diabetes. Eight studies focused on type I DM and four studies on type II DM revealed significant treatment outcomes (OR = 3.10, 95% CI [1.79, 5.38], $P < 0.0001$). 95% CI in the meantime is [3.05, 6.72] which does not intersect the invalid line OR = 1. (Fig. 7a). Meanwhile, meta-analysis leverages the number of events to investigate the effects of MSCs on different types of DM, the combined effect size of Type I is 2.56 [1.39, 4.73] and meanwhile the combined effect size of type II is 6.76 [1.83, 25.01] showing significant difference. Meta-analysis of 12 studies distributed nearly equally beside the pooled effect size and contained among the confidence intervals. This also shows the results are highly confidence (Fig. 9b).

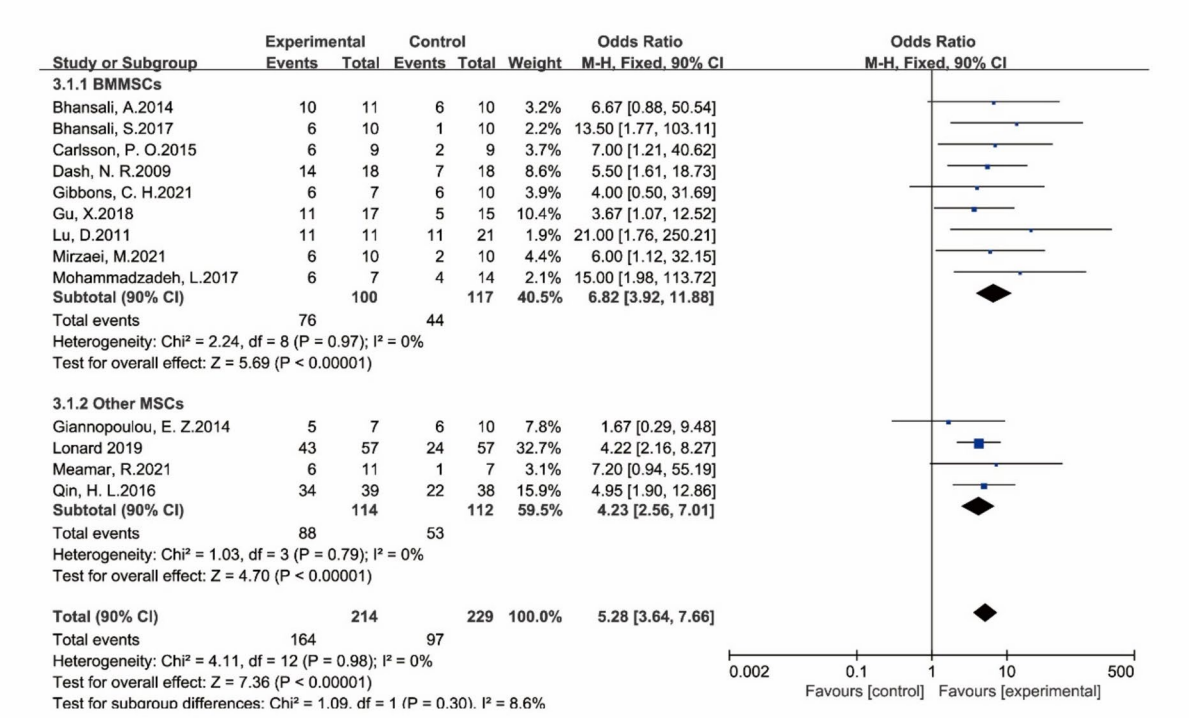
Approach of intervention

The studies included in this meta-analysis utilized various injection approaches for MSC therapy in treating DM, which may affect therapeutic outcomes (Table 2). These studies were categorized into two groups: intravenous injection and other injection (including intramuscular injection, and antecubital vein injection vessel injection). The parameters are listed as follows: The data type is dichotomous, the analysis model employed is a fixed effect model, and the effect measure utilized is the odd ratio. The individual confidence intervals and the total confidence intervals are set at 95%. The experiment groups (intravenous injection and other injections) were placed on the right and the control group was on the left in the forest plot.

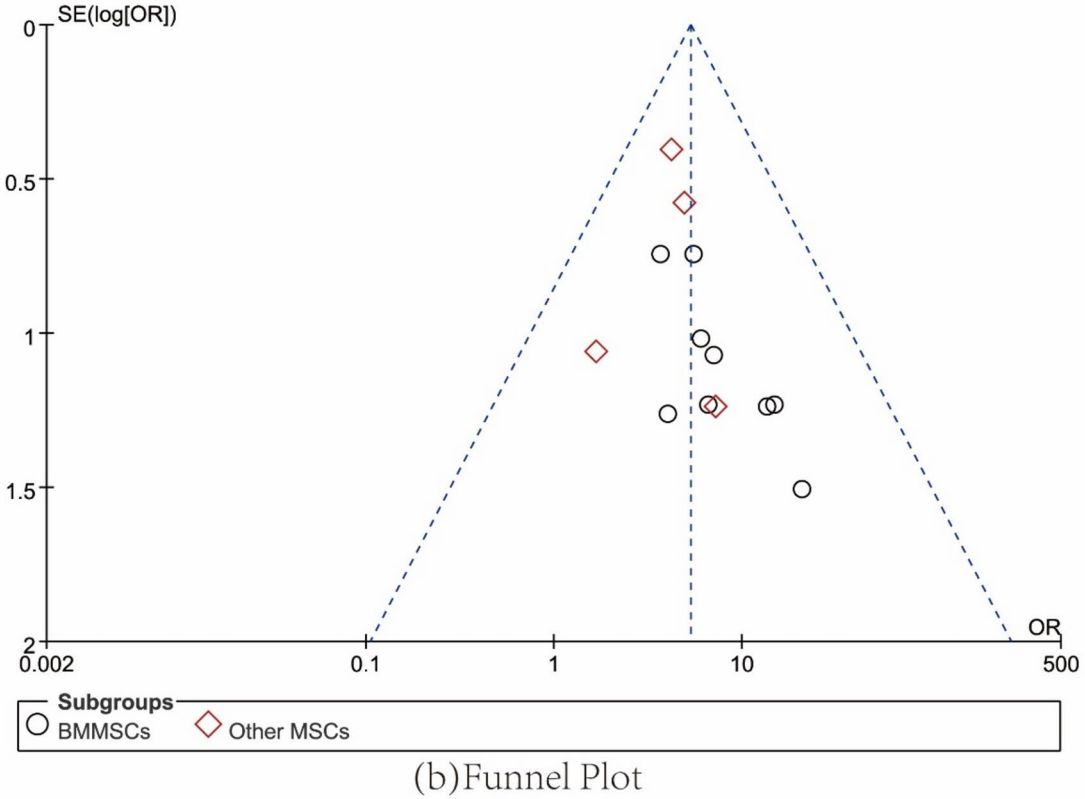
In this meta-analysis of 20 studies, twelve studies used intravenous injection and eight studies used other injection methods (e.g., intramuscular, antecubital vein). The results showed minimal variation between the two groups (OR = 4.90, 95% CI [3.21, 7.49], $P < 0.0001$). Both intravenous injection and other injection methods demonstrated similar efficacy in MSC treatment, with no significant differences ($P = 0.87$). 95% CI in the meantime is [3.21, 7.49] which does not intersect the invalid line OR = 1. $P < 0.0001$ reveals heterogeneity exists, and an I square equal to 0 is regarded as outcome reliable indicating indispensable difference among them in the process of treatment with DM. (Fig. 10a). According to the analysis, the combined effect size of intravenous injection is 4.90 [3.21, 7.49] and meanwhile other injection is 4.56 [2.23, 9.35] proving both numerical values are close to each other. (Fig. 10a). Meta-analysis of 20 studies distributed nearly equally beside the pooled effect size and contained among the confidence intervals. This also shows the results are highly confidence (Fig. 10b).

Complication of DM

In this meta-analysis of 11 studies, eight studies treated diabetic foot ulcers, and three studies treated diabetic neurological disease. The results showed minimal variation between the two groups (OR = 3.88, 95% CI [2.53,5.95], $P < 0.0001$). Both diabetic foot ulcers and diabetic neurological disease demonstrated similar

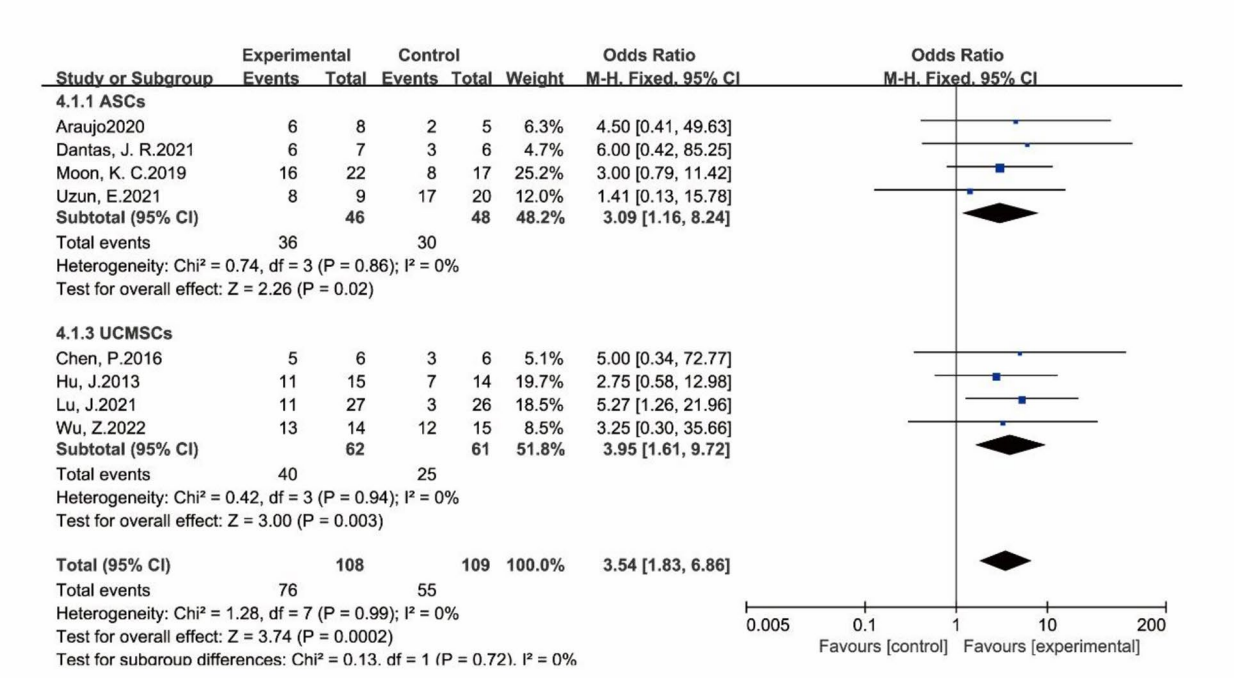


(a)Forest Plot

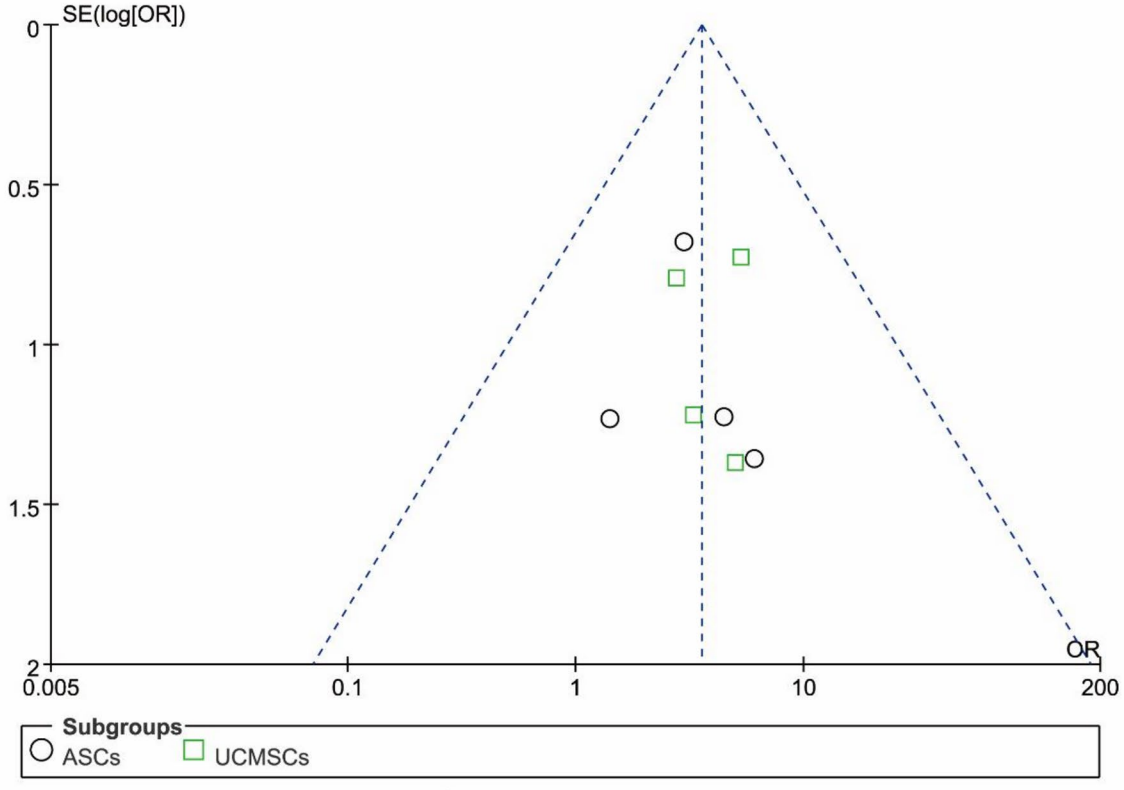


(b)Funnel Plot

Fig. 7 (**a**) stands for Forest plot. The forest plots of the included studies comparing BMMSCs and the other MSCs for treating DM mellitus. (**b**) stand for the Funnel plot. The funnel plot of the included studies comparing BMMSCs and the other MSCs for treating DM mellitus

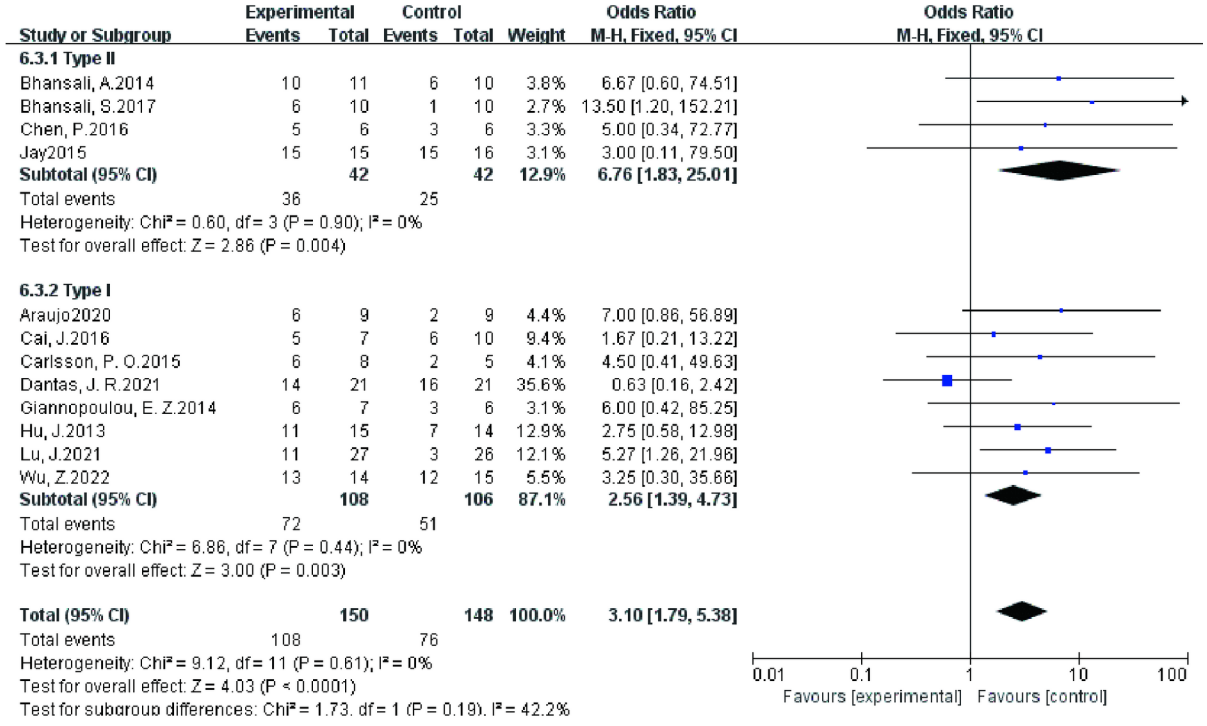


(a) Forest Plot

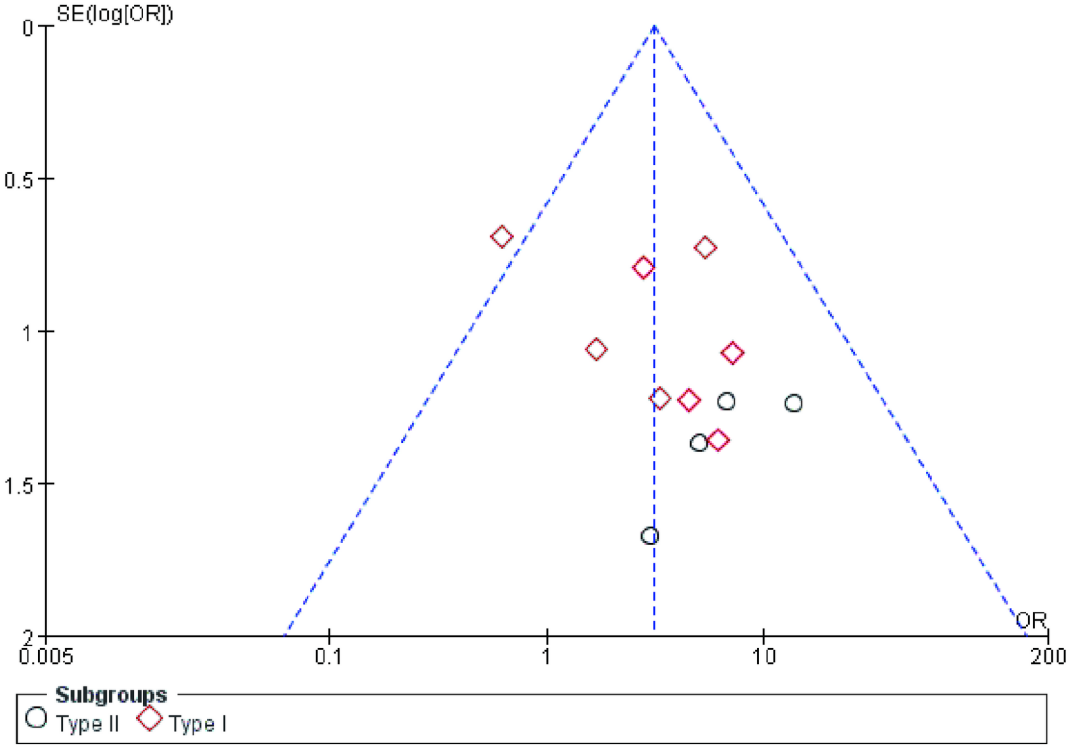


(b)Funnel Plot

Fig. 8 (**a**) stands for Forest plot. The forest plots of the included studies comparing ASCs and UCMSCs for treating DM mellitus. (**b**) stand for the Funnel plot. The funnel plot of the included studies comparing AMSCs and UCMSCs for treating DM mellitus



(a) Froest Plot



(b) Funnel Plot

Fig. 9 (**a**) stands for Forest plot. The forest plots of them included studies comparing Type I and Type II for treating DM mellitus. (**b**) stand for the Funnel plot. The funnel plot of the included studies comparing Type I and Type II for treating DM mellitus

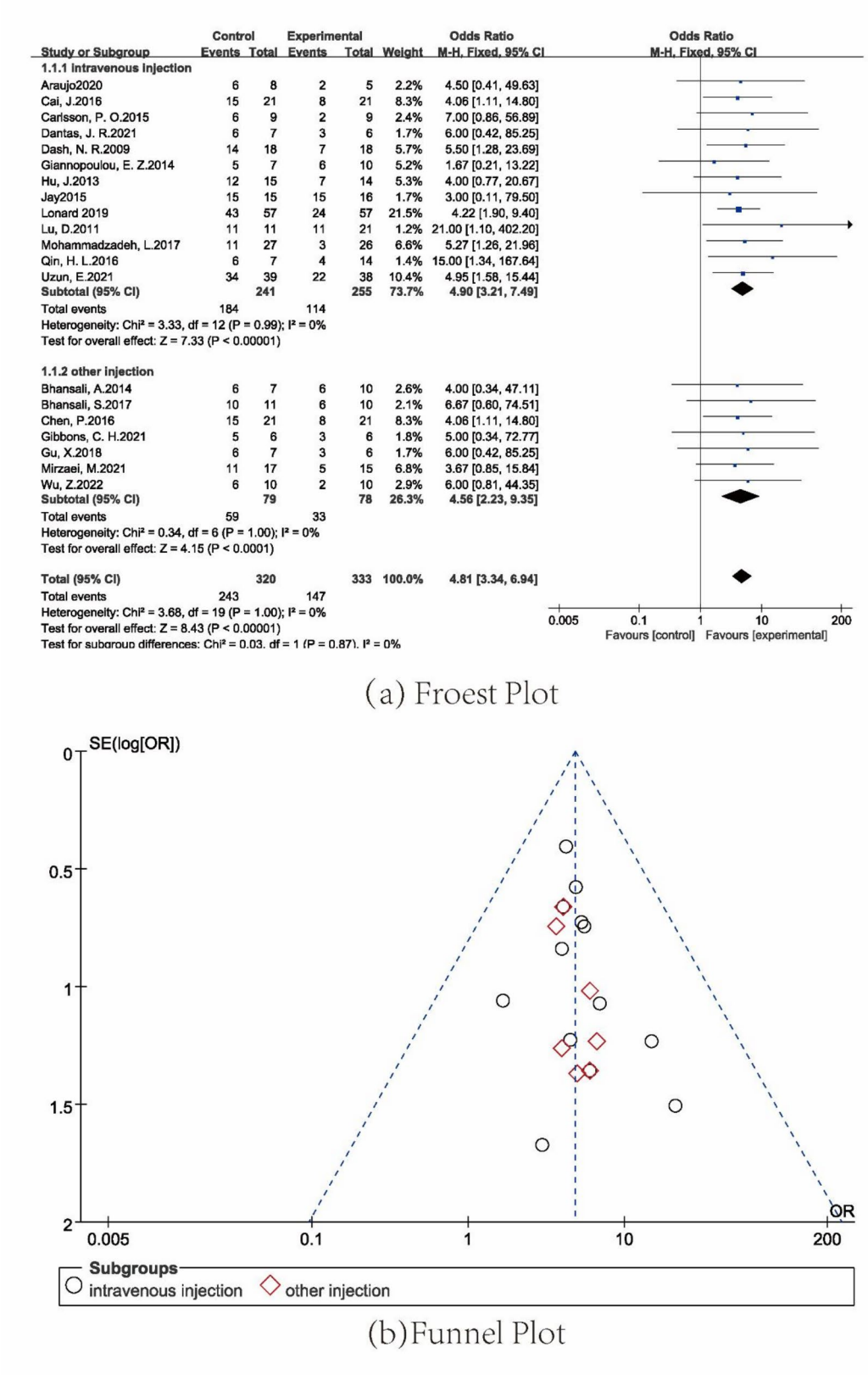


Fig. 10 (**a**) stand for Forest plot. The forest plots of the included studies compare intravenous injections and other injections for treating DM mellitus. (**b**) stand for the Funnel plot. The funnel plot of the included studies comparing intravenous injection and other injections for treating DM mellitus

efficacy in MSC treatment, with no significant differences ($P = 0.84$). 95% CI in the meantime is [2.53,5.95] which does not intersect the invalid line OR = 1. $P < 0.0001$ reveals heterogeneity exists, and an I square equal to 0 is regarded as outcome reliable indicating indispensable difference among them in the process of treatment with DM. (Fig. 11a). According to the analysis, the combined effect size of diabetic foot ulcers is 3.81 [2.39, 6.07] and meanwhile diabetic neurological disease is 4.29 [1.48, 12.42] proving both numerical values are close to each other. (Fig. 11a). Meta-analysis of 11 studies distributed nearly equally beside the pooled effect size and contained among the confidence intervals. This also shows the results are highly confidence (Fig. 11b).

Discussion

This is the first meta-analysis discussion MSCs from the perspective of autologous, allogenic and sources et al. A number of clinical cases from the meta-analysis raise the possibility of MSCs and DM furtherly, 4257 articles were collected and eventually, 35 were reserved with requirements for inclusion criteria carried forward collection. Besides, a total of 83 items were collected on the website of ClinicalTrials.gov which involved all the MSCs and all the DM and its complications. The risk of bias graph and bias summary are also presented which reveals the distribution of the risk to determine whether the clinical cases are inclusive.

Safety and efficacy

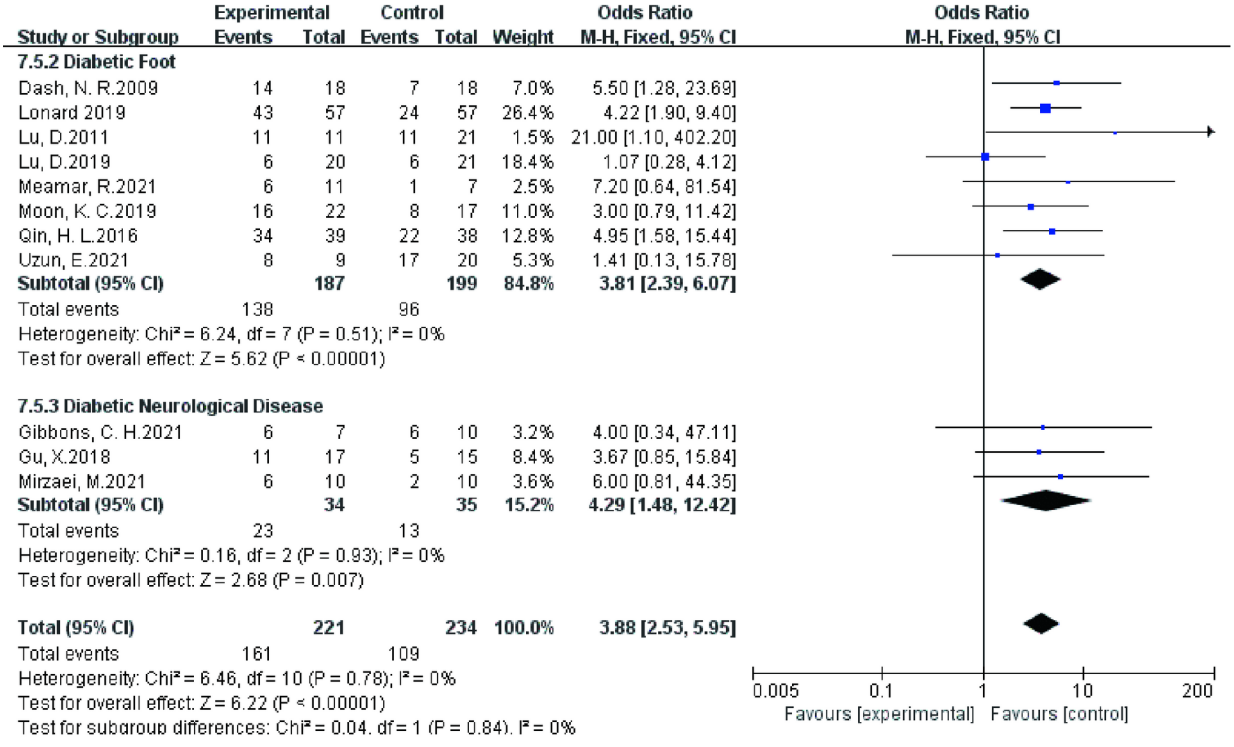
MSCs are compared with placebo to analysis whether they are utilized safely. The outcomes (OR = 2.79, 95% CI [1.63, 4.75], $P = 0.0002$) of the meta-analysis verified that MSCs are equipped with high safety. The confluence effect size of nearly all included studies is greater than 1 and all included studies are located inside the funnel plot, and a large portion of 95% confidence intervals were in contact with 1 elucidating MSCs are consistent with placebo in terms of safety. Placebos is a substances with inert and non-toxic, the major ingredients are starch and glucose which are only the same size, color, smell, and appearance as laboratory medicine [61]. Moreover, the MSCs are identified as features with stronger security from the perspective of forest plots and funnel plots. In recent years, a large amount of extraction technology such as flow cytometry, ficoll-isolated, and gas-liquid separation [62] have emerged and aroused the purity of MSCs exhibiting stronger security. Management of the production and standards control MSCs increasingly strictly, so the more purity MSCs are appropriate for drug safety. Another reason is low immunogenicity. MSCs are capable of interact with immunomodulatory factor such as TGF-β, HGF and IL-10 to restrain immunological activity and reduce the risk of immunological exclusion. Besides, MSCs manage to interact with diverse populations of immunological cell to influence proliferation and diminish allogenic immunological cell exclusion [63]. In addition, an important factor anti-apoptotic is that the extent to which are beneficial to protecting surrounding cells and decreasing immune-mediated damage [64], the anti-apoptotic factor includes VEGF165 and FGF-2,ertc which is secreted by MSCs. In all, low immunogenicity and anti-apoptotic are in favor of drug safety.

MSCs are compared with SCT - Common standard clinical treatments - to analysis whether they are leveraged better than SCT. The outcomes (OR = 4.12, 95% CI [2.76, 6.14], $P < 0.0001$) of the meta-analysis verified that MSCs are more effective than SCT in terms of DM and are qualified to be utilized as a clinical drug. MSCs with the confluence effect size of 4.12 units are more effective than SCT revealing the possibility of being provided with enough treatment potentialities with respect to MSCs. The clinical method in DM mainly consists of insulin injections, etc. So, it is defined as SCT by us. With the method of subcutaneous insulin injection into the body, absorbed by the capillary so that the small molecules have the competence to enter into the blood vessels, secondly with the blood circulation flows through the whole body to benefit of promoting the utilize of glucose transporter proteins for shrinking blood glucose. However, this treatment strategy has significant drawbacks, first of all, long-term insulin injection may cause the danger of hypoglycemia even ketoacidosis [65], long-term injection capable of falling hepatic glycogen reserve, and organ atrophy, dehydration and function decrease also occur with age. Besides, a decrease in gluconeogenesis might cause dizziness, nausea, and weakness. Second, injecting insulin at the same site for a long period may be favorable for subcutaneous fat growth, which influences insulin absorption and blood glucose control [66]. What's more, long-term insulin injections can potentially diminish the body's natural regulatory mechanisms, as diabetic patients often require lifelong treatment leading to a reliance on external insulin regulation.

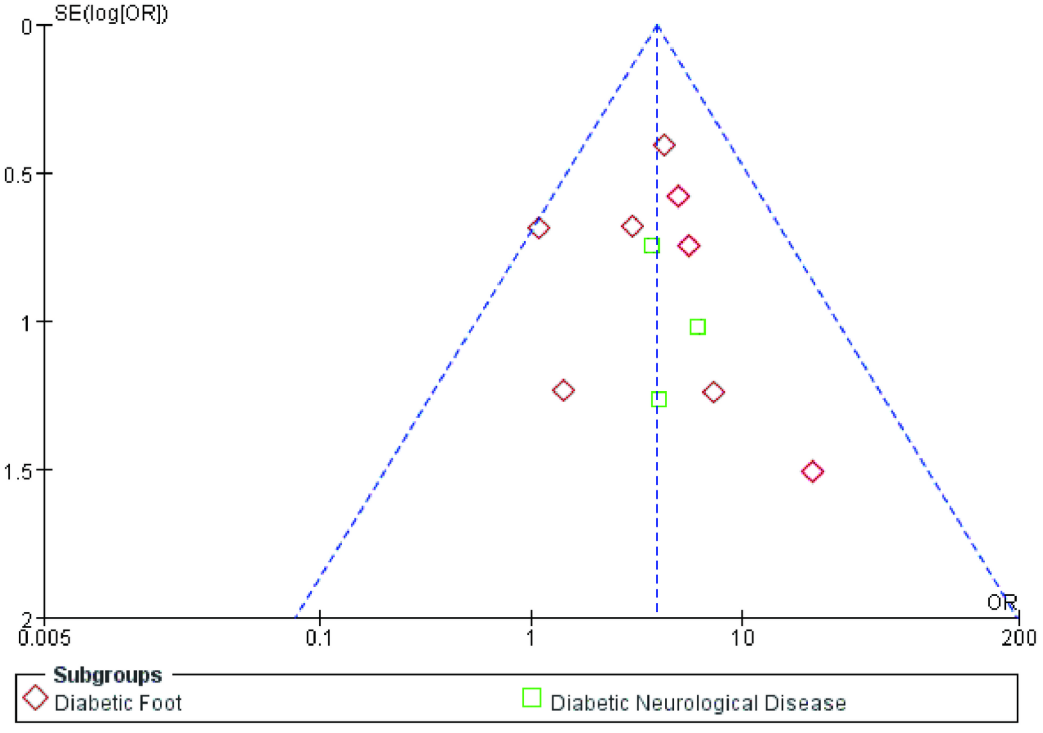
Immunomodulation: MSCs vs. monocytes

Both monocytes and MSCs exhibit multifunctionality, which they have the competence to differentiate into diverse cell types and play crucial roles in therapeutic applications.

Hepatocyte Growth Factor (HGF), Insulin-Like Growth Factor (IGF) and Exendin-4 are three biomolecules associated with cell growth, repairment and metabolism. They all exist in MSCs but not in the monocytes [67]. Meanwhile, they are equipped with similar mechanisms. First, they all have the benefits of cell signaling. HGF connects with c-Met receptor activating downstream signaling [68], IGF fosters stem cell division and differentiation



(a) Froest Plot



(b) Funnel Plot

Fig. 11 (**a**) stand for Forest plot. The forest plots of the included studies compare diabetic foot ulcer and diabetic neurological disease for treating DM mellitus. (**b**) stand for the Funnel plot. The funnel plot of the included studies comparing diabetic foot ulcer and diabetic neurological disease for treating DM mellitus

by activating IGF-1 receptor downstream signaling [69], Exendin-4 as a GPL-1 receptor agonist has the ability to Enhance insulin secretion and inhibit glucagon release [70]. Second, they are all equipped with anti-inflammatory mechanisms and protect the βcell from autoimmune attack. IGF refrain the production of proinflammatory factor, Exendin-4 reduce the Oxidative Stress Response and upgrade DM microenvironment [71]. Third, they have further facilitated neovascularization and improved microcirculation to reduce the possibility of DM complications [72].

The outcomes (MD = 6.52, 95% CI [3.56, 9.48], $P < 0.0001$) through continuous variable meta-analysis accounts for MSCs are preferred to monocytes in terms of treating DM. As a mature blood cell, monocytes are a subpopulation of leukocytes, which account for 3–10% of all leukocytes in adults [73]. It originates from Common Myeloid Precursors (CMP) in the bone marrow, and subsequently, they mature and enter the peripheral circulation [73]. There have been many breakthroughs in the investigation of monocytes in recent years. In 2019, Prof. Florent Ginhoux et al. investigated the development of monocytes that play a critical role in the bone marrow and the renewal of macrophages in adult tissues. In 2021, researchers at the University of Liège, Belgium, identified that monocytes have also the capacity to proliferate locally. In 2024, Steffen Jung's team proposed that the individual evolution of classical monocytes determines their function and effect as tissue macrophages [74]. However, monocytes are confronted with difficulties in regulating the immune response directly because of monocytes functional heterogeneity, viral inhibition and complexity of the inflammatory environment [75]. Monocytes also play an important role in the treatment of DM. It not only has the ability to enrich C-peptide secretion and decrease HbA1C levels but also has the potency to target specific subpopulations for treatment [76]. However, A number of research perspectives raise the doubt of monocyte efficacy in DM. First, there might exist an enormous difference between the short-term effect and the long-term effect of monocytes in the process of treatment. In the experiment by Prof. Zhou et al., it was pointed out that subjective symptoms would be promoted after treatment for 3 months, including resting pain, limb coldness score, and numbness et al., but objective indicators such as intermittent claudication distance, lower limb skin temperature, transcutaneous partial pressure of oxygen TcPO2 and resting ankle-brachial index ABI needed to be changed even after 6 months. Second, the transplantation dose of monocyte cells did not affect the treatment outcome. The researchers found that concentrations of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) did not transform significantly after 6 months of transplantation [77]. Finally, endothelial cell aging has a great effect on the migration speed leading to the senescence of monocytes, and the secretory properties change greatly, and eventually, it contributes to the occurrence of vascular complications in monocytes [27]. In conclusion, MSCs have a significant advantage over monocytes in carrying growth factors and peptides, which play a crucial role in promoting cell proliferation, inhibiting apoptosis, regulating the immune system, and ameliorating blood glucose and insulin resistance.

MSCs vs. iPSC

There are a great number of DM treatment strategies, such as surgical pancreas transplantation, and gene therapy in clinical treatment [78]. Nevertheless, they are facing the situation of either scarce donors or their safety, and hence brand-new tactics—— induced pluripotent stem cells (IPSCs) are adopted in clinical research, resulting in light safety and ethical issues by recoding somatic cells. The diseased iPSCs are generated by extracting tissue cells (somatic cells) from DM patients, overexpressing transcription factors (OCT4, KLF4, SOX2, c-MYC), secondly they are modified into correct iPSCs through CRISPR/Cas9, and finally inducing them to differentiate into beta cells [79]. On the one hand, it can be injected into the human body, and on the other hand, it is capable of being used for disease model screening, gene editing, and cell therapy [80] and the iPSCs have a low carcinogenic rate in comparison to the Embryonic stem cells. So far, four clinical trials using stem cell-derived pancreatic cells to treat T1D have been registered (NCT03162926 (completed), NCT03163511 (recruited), NCT02239354 (active, not recruited), and NCT02939118 (invited) [81].

MSCs are of critical importance in treating DM compared with iPSCs. Firstly, it has the ability to transdifferentiate into a variety of mesodermal cell types, such as osteoblasts, chondrocytes, adipocytes, endodermal and ectodermal cells under certain conditions [82]. Besides, MSCs have also been shown to be a good source to differentiate into other non-mesodermal cell lineages, such as neuronal cells or hepatocytes, under specific conditions. The differentiation capability offers MSCs great potential for utilization in regenerative medicine and tissue engineering [83]. They are capable of being employed to repair or replace damaged tissues to treat DM. Secondly, MSCs, equipped with less immunogenic, have a lower risk of chromosomal abnormalities during in vivo culture, and are routinely easier to culture and expand in vivo than iPSCs. Furthermore, MSCs even have homing ability to migrate to damaged tissues [84] helping them to repair. Finally, MSCs cost less than iPSCs, the pure iPSCs are acquired with the methods of adding induction factors first secondly isolating them by flow cytometry and finally clustering in the single-cell plate. However,

the transformation success rate of the induction factor is only 1% leading to low production and efficiency [85], and the flow cytometry has the disadvantages of sophisticated operation and is disturbed easily by fluorescent [86] contributing to high cost.

Autologous and allogeneic

MSCs are categorized as Autologous MSCs and Allogeneic MSCs based on their source and application. What is better among them could be identified according to the meta-analysis, Autologous inclusion of 214 cases appear in the experimental group and 229 cases in the control group, the OR of 5.28 indicates that the event rate in the autologous treatment group was 5.28 times higher than that in the control group. Allogeneic inclusion of 123 cases displayed in the experimental group and 125 cases in the control group, and meanwhile they have the OR of 3.52, elucidating that the event rate in the treatment group was 3.52 times higher than the control group. Autologous MSCs refer to the cells extracted, isolated, and amplified from the subjects' tissue, which is consistent with the immune system of the participant's tissue and does not cause immune rejection [87]. Autologous MSCs are conducive to immunomodulatory [22] and anti-inflammatory cytokines comparing to Allogenic MSCs [23]. Firstly, MSCs form vascularization and contribute to matrix deposition by producing VEGF and FGF, a kind of growth factor, and stimulating proliferation and differentiation when localized wound inflammation and hypoxia [87]. Secondly, MSCs are identified as low immunogenicity owing to the low level of MHC class I molecules, such as β2-microglobulin, Peptide Loading Complex(PLC) and Heat Shock Proteins(HSPs), expressed on the surface of MSCs, reducing the likelihood that they will be recognized and attacked by the host immune system [88]. Thirdly, MSCs are capable of inducing immunosuppressive cells, such as regulatory T cells to help suppress excessive immune responses [89]. Prostaglandin E2 (PGE 2) secreted from MSCs holds the ability to suppress inflammatory cytokine produced from macrophage. IL-10 plays a prominent role in dampening Th1and Th17 and modulates Dendritic Cell (DC) to reduce inflammatory and immunological response [90]. Conversely, Allogeneic MSCs, extracted from the tissue of another subject, might further facilitate autoimmune rejection which is not beneficial to repairing the production of islet B cells [91]. Besides, there may be ethical issues concerning the sourcing and utilization of Allogeneic MSCs, particularly facing the clinical patients. In short, Autologous MSCs are more effective than Allogeneic ones majorly thanks to their low immunogenicity.

Autologous MSCs are also diversified into BMMSCs, ASCs and UCMSCs. According to the results of meta-analysis, there are 100 cases in the experimental group and 117 cases in the control group, and the OR was 6.82. In the group of Other MSCs, there were 114 cases in the experimental group and 112 cases in the control group, and the OR was 4.23. The final analysis results of them are mirrored in finding BMMSCs perform better than other sources. BMMSCs usually originated from adult bone marrow, and they are in the acquisition by bone marrow aspiration. The BMMSCs appear to the merits of high security, easy acquisition, and differentiation ability, they are accompanied by an abundant range of sources and mature acquisition techniques [91] and they all complete the potential of multiple differentiation and the advantages of immune regulation and are regularly applied in the treatment of DM [92]. IL-10 and EGF from the BMMSCs adverse to the expression of inflammation-related cytokines such as IL-6, MCP-1, TNF-α and IL-1 to prevent diabetic nephropathy. However, Unlike BMMSCs, ASCs, absorbed from the adipose tissue with the methods of liposuction surgery, are greatly influenced by the sources of different body parts leading to the differences between different donors [93]. Moreover, cellular senescence is more likely to occur which greatly influences proliferative and differentiation capacity during the process of vitro culture [93]. Overall, BMMSCs offer novel insight into the treatment of DM in the aspects of significant improvements in blood sugar control, insulin requirements, and HbA1c levels, despite a great number of barriers—invasion and limitation etc.—continue to be addressed urgenly [94],.Thus, while promising, optimizing treatment protocols is a crucial research approach for maximizing MSC therapy's efficacy in DM.

Allogeneic ASCs and UCMSCs have broadly affected the clinical trial of DM owing to high safety and a wide range of treatments. In the process of meta-analysis, the sample size and number of events are nearly equal. In ASCs, there were 46 cases in the experimental group and 48 cases in the control group, with an OR of 3.09, showing that the event rate in the ASCs treatment group was 3.09 times higher than in the control group. In UCMSCs, there were 62 cases in the experimental group and 61 cases in the control group, with an OR of 3.95, proving that the event rate in the UCMSCs-treated group was 3.95 times higher than that in the control group. The potential causes may be as follows. In Allogeneic MSCs, researchers rarely utilize bone marrow for two major reasons: First, although bone marrow puncture technology is widely provided, it is rough to extract and separate, and the damage caused to subjects is difficult to compensate, thus subjects are reluctant to acquire MSCs from bone marrow; Second, bone marrow, a highly special microenvironment, mainly contains hematopoietic stem cells and red blood cell precursors playing a crucial role in maintaining the balance of the blood system and regulating the function of the immune system [95]. ASCs are

capable of being obtained by liposuction, which greatly reduces the damage to participants. Compared with BMMSCs, the ASCs display stronger proliferation ability, and they also have the competence to be fused by methods of gene modification [96]. They are even eligible to coordinate and target the regulation of glucose and lipid metabolism. However, there also exist several issues, such as large individual differences and poor heterogeneity [97], and it is puzzling to develop standardized indicators to ensure the quality and consistency of cells. UCMSCs mainly have the function on the target organs of insulin, such as the liver and fat, etc. With low immunogenicity, UCMSCs are primarily adopted in the treatment of type II DM, whose safety and efficiency during the period of treatment are confirmed [98]. The OR of UCMSCs was larger than that of the ASCs slightly, indicating that the therapeutic efficacy of UCMSCs may be better than that of ASCs slightly, but the two were not significantly different. Nevertheless, UCMSCs, like the ASCs, are also trapped in the severe problem of standardization and the similar characteristics of ASCs and UCMSCs may be the reason for their similar efficacy. Although there exists some issues in UCMSCs, acquisition approach easily and fabrication sales largely promotes it prevalent comparing with two other allogenic MSCs.

Besides treating DM directly, MSCs have been extensively performed for the complication, participially in the Type I DM and Type II DM, and their pathogenesis has been described in depth previously [99]. According to meta-analysis, there were 108 cases in the Type I experimental group and 106 cases in the control group with an OR of 3.10. There were 42 cases in the Type II experimental group and 42 cases in the control group with an OR of 6.76. The OR value of Type II was higher than Type I, indicating that MSCs were more effective in treating Type II. The data offered novel insight into DM, which MSCs are the most effective treatment for Type II DM. From the perspective of the above figure, MSC therapy elucidates the best effect in the treatment of type II, which is judged as one of the common complications of DM [100].

Approach of intervention

MSCs are divided into intravenous injections and other injections depending on the different injection methods in meta-analysis. The number of experimental events included in the intravenous injection is 241 and the number of control events is 255, with an OR value of 4.9. In the other injection method, the number of experimental events is 79 and the number of control events is 78, with an OR value of 4.56. The overall superiority ratios of the two injection methods were similar, indicating that the therapeutic effects of the two injection strategies were similar. Intravenous injection, belonging to the systemic injection, is the most common and has broadly affected the clinical trial of DM profoundly owing to the high safety and convenience of treatment. Intravenous injection is the method of injection via intravenous to deliver drugs throughout the body, it not only brings out the full potential of a drug rapidly which affords to reach its peak when they are injected simultaneously but is also equipped with high bioavailability as well is precise and controlled dosage. It also exists fatal disadvantages–highly specialized and risky, intravenous injections may pose a risk as well as complications due to mishandling, such as phlebitis, leakage, and overdose. Whatmore, there is a great deal of uncertainty about the half-life for intravenous injection MSCs, only a small number of MSCs via intravenous injection are adequate to pass through the lungs in comparison to the mostly filtered and removed by the lungs and the cells reach the spleen and liver after 48 h and the whole body after 10 days. The other injection belonging to non-intravenous injection has similar features, taking the example of intramuscular injection, it is identified as fast-acting and highly bioavailable [101], what more it is equipped with first pass effect which contributes to better utilization of cells, nevertheless it would cause serious damage and risk of infection. Above all, Intravenous injection is equipped with similar effects compared with other non-systemic injection and exists several drawbacks, therefore, optimizing the route of injection, improving cell quality, determining the optimal dose, and choosing the right timing of treatment are paramount to improving the efficacy of MSC therapy.

Efficiency of different complication

MSCs have a favorable effect on different complications, especially in diabetic foot ulcers and diabetic neurological disease. According to meta-analysis, the number of experimental events included in the diabetic foot ulcers is 187 and the number of control events is 199, with an OR value of 3.81. In diabetic neurological diseases, the number of experimental events is 34 and the number of control events is 35, with an OR value of 4.29. The overall superiority ratios of the two complications were similar, indicating that the therapeutic effects were similar. Diabetic foot ulcers are a common DM complication in clinics and the main reason is the deficiency of vascular endothelial cells [102]. The MSCs are equipped with the ability to repair impaired cells with the methods of promoting NO release, fostering VEGF and PGI2, which is in favor of vasodilating blood vessels and inhibiting platelet activation and aggregation [103]. Diabetic neuropathy is a common chronic complication of diabetes and damages the peripheral nervous system and causes a series of dysfunction and clinical symptoms under chronic hyperglycemia environment [104]. MSCs are conducive to secreting anti-inflammatory cytokine IL-10 and adverse

to the level of pro-inflammatory factor TNF-Aand IFN-γ [105].Above all, MSCs have shown significant potential in the treatment of both diabetic foot ulcers and diabetic neurological disease.

Prospectives

Stem cell therapy holds a promising future in treating DM, particularly MSCs playing a pivotal role [106]. MSCs have shown potential in modulating immune responses, protecting pancreatic beta cells, and improving the islet environment, which can alleviate symptoms of DM. In our research, MSCs present stronger safety and therapeutic efficacy than existing clinical protocols and are extraordinarily effective in Type II DM, Autologous MSCs are more effective compared to Allogeneic, and Autologous bone marrow MSCs are more notable comparing favorably with the other autologous stem cells and the effect is not significant among Allogeneic MSCs.

However, there is still a challenge to be addressed urgently. The cost of MSC therapy is relatively high, requiring specialized equipment and technicians from MSCs collection, cultivation to the treatment process, in addition to the current cell culture technology which is difficult to meet the demand for large-scale clinical application [107]. Enormous variability of sources requires strict quality management practices during the process of production, in order to avoid instability in the therapeutic effect because of MSCs batch variation, the MSCs quality and consistency should be ensured [108]. Although theoretically MSCs are capable of triggering low immune response, their immune properties may vary due to environmental factors, so the strict GMP standards need to be perfected and adhered to mitigate environmental influences [109]. Strengthening cooperation and communication between different countries and regions is critical for the development of MSCs for DM, more effective GMPs can be developed and existing production management mechanisms can be completed to ensure the safety of MSCs and make them safer and more effective treatment for DM through sharing research data and experience [110].

Although MSCs have terrific therapeutic effects, a large number of surveys encountered a situation where MSCs have a low survival rate [111] and poor transformation efficiency in diabetic patients [112], Is it possible to explore alternative methods or strategies to enhance the functionality and efficiency of MSCs, taking into account various factors that could influence their performance and therapeutic potential? Exosome extracellular lipid nanovesicles, with a diameter between 30 nm and 200 nm, are stimulated by physical or chemical means [113]. MSC endocytosis is usually prescribed to produce early sorting exosomes first and next process to form late sorting exosomes, and finally excreted out of the body [114]. Meanwhile, a large number of microRNAs and proteins are carried by exosomes to be conducive to forming Islet B cells [115]. Exosomes are a major source for the treatment of DM and they have also the capacity to reduce oxidative reactions [116], prevent apoptosis [117], improve insulin sensitivity, and regulate cellular homeostasis [118] offering a novel insight into the treatment of DM.

Exosomes feature a wide range of sources, relatively stable structure, long storage time, easy absorption through the blood-brain barrier, and may promote human immune response [119], the exosomes provide a good strategy for treating DM. However, the repair directed to the DM does not mainly depend on the proliferative system, but on the paracrine system repair [120]. The paracrine system refers to a hormone delivery method of the cells that work on the neighboring cells by diffusion, it influences the cell function activates by sending the message to local organization [121], Exosomes as a means of paracrine communication are adequate to change the function of white cells and result in vascular dysfunction to achieve intercellular signaling. The miRNAs carried by exosomes show the character of short length, high sensitivity, and fast reaction speed and they come from a wide range of sources. The most important is that they are capable of being used as a marker for DM [122], which will be beneficial for the identification of DM. Exosome miRNAs regulate AKT3 [123] and HMGB1 genes triggering the occurrence of DM mellitus and complications, such as retinopathy, cardiovascular, peripheral neuropathy, diabetic foot ulcers, nephropathy, and macrovascular complications et al.

MSCs are not readily recognized by host T cells on the surfaces because of the low level of MHC class, I molecules expressing, which can avoid recognition by homozygous allogeneic response cells, and thus they have low immunogenicity. At the same time, MSCs are equal to suppress both intrinsic and adaptive immune responses. Exosomes, as small extra membranous vesicles secreted by MSCs, have similar immunomodulatory functions. Nevertheless, they hold the advantage of a lower possibility of immune rejection, greater penetration capacity, and avoidance of the danger associated with cell transplantation [124]. Modifying MSCs has the competence to improve and promote the application of exosomes in DM and diabetic complications. However, exosome-encapsulated MSCs still face several bottlenecks in the current clinical research. For example, exosomes have relatively low yield and limited efficacy, and the stability and storage conditions are probably relatively harsh [125], exosomes also have the potency to be removed by the immune system and create many difficulties to be used as carriers for targeted delivery of biomolecules secreted by MSCs [126]. Despite the current challenges that exist

in the research and application of exosome-encapsulated MSCs, there is no denying the great potential and promise of exosomes to treat DM.

Additionally, while MSCs have presented advantages in clinical trials, The trajectory of its cellular activity within the individual, the function it performs, the final destination are not fully understood and require further research. The employment of MSCs in DM is an area of active investigation, and accompanying with our understanding of these stem cells and their interactions with the diabetic milieu deepens, so does the potential for developing effective stem cell-based therapies. As the field progresses, MSC-based treatments will probably become an integral part of the DM treatment landscape, offering patients a new avenue for managing their condition and perfecting their quality of life. Hence, MSCs are eligible for searching the proper cell type for the better DM therapeutic effect which is responsible for helping clinical researchers to understand and cure DM in a huge number of patients with disorders and injuries.

Conclusion

Above all, MSCs are judged as crucial during the process of treating DM, they have the competence to treat DM safety and efficiency and are more conducive to Diabetic foot lower limb comparing with monocyte. Further analysis, Autologous performs better than Allogenic, BMMSCs are the best among all Autologous MSCs and there exists no apparent difference between Allogenic MSCs. The healing effect of Type II is identified better than Type I when MSCs are applied, the difference among approach of intervention and variance between different complications are nearly few. Besides, exosomes and iPSCs have also the capacity to treat DM because of paracrine system and high differentiation capacity, despite there is nearly no clinical studies currently. All the research outcomes offer a novel insight into treatment DM and provide valuable guidance for physicians clinical applications.

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Data availability
Data will be made available on request.

Declarations

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Not applicable.

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Not applicable.

Competing interests
The authors declare that there are no conflicts of interest.

Author details
[1]National "111" Center for Cellular Regulation and Molecular Pharmaceutics, Cooperative Innovation Center of Industrial Fermentation (Ministry of Education & Hubei Province), Hubei University of Technology, Wuhan 430068, China
[2]Wuhan Vickor Medical Technology Co. Ltd., Building 3–3, 3–4, and 3–5, Zhaoshang·High-Tech Network Valley, No. 16, Luzling Third Road, East Lake High-Tech Development Zone, Wuhan (Wuhan Area of the Pilot Free Trade Zone), Wuhan 430015, China

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