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REVIEW

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Human studies of the efficacy and safety of stem cells in the treatment of diabetic peripheral neuropathy: a systematic review and meta-analysis

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Abstract

Objective To assess the efficacy and safety of stem cell therapy in human studies for diabetic peripheral neuropathy (DPN).

Methods A comprehensive literature review was performed across multiple databases, including Ovid MEDLINE ALL, Embase via Ovid SP, Scopus, Web of Science Core Collection, and Cochrane CENTRAL, up to January 31, 2024. Keywords and controlled vocabularies related to diabetic neuropathy and stem cell therapy were used. Inclusion criteria encompassed all controlled trials examining stem cell therapy for DPN, excluding animal or in vitro studies, review papers, conference abstracts, and editor letters. Data extraction and risk of bias assessment were independently performed by multiple reviewers using standardized tools.

Results Out of 5431 initial entries, seven were included. Stem cell therapies included bone marrow-derived mononuclear cells and umbilical cord-derived mesenchymal stem cells, administered mainly via intramuscular transplantation. Meta-analysis indicated significant improvements in motor nerve conduction velocity (weighted mean differences (WMD): 2.2, 95% CI 1.6–2.8) and sensory nerve conduction velocity (WMD: 1.9, 95% CI 1.1–2.6). Vibration perception threshold and Toronto Clinical Scoring System scores decreased significantly (WMD: − 2.9, 95% CI − 4.0, − 1.8, and WMD: − 3.6, 95% CI − 5.0, − 2.2, respectively). Sensitivity analysis and subgroup analysis confirmed the robustness and specificity of these findings. The complications were pain and swelling at the injection sites, which disappeared in a few days.

Conclusion Stem cell therapy shows significant promise in improving clinical outcomes for DPN, with evident benefits in nerve conduction and sensory parameters. Further research is needed to consolidate these findings and optimize therapeutic protocols.

Keywords Diabetic neuropathy, Adult stem cell, Umbilical cord blood stem cell transplantation, Bone marrow cell transplantation, Meta-analysis

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Introduction

Diabetes mellitus (DM) is the most significant worldwide epidemic of the twenty-first century, with the International Diabetes Federation reporting that it affects 425 million individuals globally, particularly in developed countries [1, 2]. Diabetes is associated with numerous complications, with diabetic peripheral neuropathy (DPN) being the most prevalent, although often neglected, and manifesting early in diabetic patients [1–3]. DPN is diagnosed in approximately half of all diabetic patients [4].

DPN, characterized by symptoms and signs of peripheral nerve impairment in individuals with diabetes after ruling out other causes, can lead to diabetic foot complications, including infections, ulcers, and limb amputations [5, 6]. Initially, DPN impacts the sensory nerves symmetrically in the distal regions of the lower extremities. The primary strategies for preventing DPN are maintaining glycemic control and implementing lifestyle modifications [1].

To date, no curative therapy exists for DPN, necessitating a pharmacological approach for its management [1, 7]. Various types of drugs are available for DPN, including anticonvulsants such as pregabalin, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), opioid receptor agonists, and topical medications like capsaicin and lidocaine [8–12]. Recently, gene therapy and cell therapy have emerged as two promising strategies for the therapeutic management of DPN [3, 13].

Stem cell therapy, utilizing various types like bone marrow-derived, embryonic, pluripotent, endothelial progenitor, mesenchymal, or dental pulp stem cells, is considered a promising regenerative approach to potentially treat or halt the progression of DPN. This is due to their ability to regenerate tissues and secrete factors such as angiogenic and neurotrophic factors [1, 14]. Over the past decade, studies have shown that stem cell transplantation effectively treats DPN in experimental diabetes across diverse animal models [15, 16]. However, there remains limited knowledge regarding its therapeutic effects on humans.

In this systematic review and meta-analysis, we assess the efficacy and safety of stem cell therapy in human studies for DPN. Our goal is to evaluate stem cell therapeutic outcomes in human subjects, aiming to improve research quality and advance clinical applications for DPN treatment.

Materials and methods

Search methodology

The review followed the population, intervention, comparison, outcome, type of question and type of study design (PICOTT) framework to define the research question and eligibility criteria, and it was reported using the PRISMA 2020 statement [17]. A systematic search was conducted in Ovid MEDLINE ALL, Embase via Ovid SP, Scopus, the Web of Science Core Collection (SCIE, SSCI, and ESCI), and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid SP. The search included all available articles from the start of these databases until January 31, 2024. The study utilized keywords such as diabetic neuropathy, stem cells, and cell transplantation, together with controlled vocabularies such as Medical Subject Headings (MeSH) and Excerpta Medica Tree (Emtree), without any limitations on time or language. The reference list of pertinent review articles was examined to locate other relevant articles. The search approach and keywords are outlined in Table S1.

Study selection

First, duplicate records were eliminated, and the remaining references were uploaded into the Rayyan web-based application for systematic reviews [18]. Three authors (SJ, MRZR, and ZB) individually examined all titles and abstracts from the search results to identify papers that may satisfy the qualifying requirements. All controlled trials, whether randomized or non-randomized, that examined the efficacy and safety of stem cell therapy for the treatment of diabetic peripheral neuropathy (DPN) with DM-1 or DM-2 were included in the study. The exclusion criteria encompassed animal or in vitro experiments, as well as study procedures, review papers, conference abstracts, and letters to editors. Then, they compared their screening results. Studies were excluded if all the reviewers agreed to exclude them, and they moved to full-text screening if all decided to keep them. In cases of disagreement, the reviewers had a meeting in which each reviewer explained his/her reason, providing context for the discrepancies. Then they discussed and agreed on whether to exclude or retain the study. After the initial screening, the authors conducted a comprehensive review of the full texts of all selected studies and applied eligibility criteria independently before comparing results again. The fourth reviewer (SDA) reviewed the selections to resolve any inconsistencies or disagreements through discussion sessions with the other reviewers. The reviewers worked together to reach a consensus and found a common agreement. For example, the two key challenges were faced for articles that used stromal cells without explicitly mentioning stem cells and articles that used stem cell-derived exosomes. Since the main focus of the study was on the effects of stem cells specifically, and stromal cells are not necessarily stem cells, while exosomes are vesicles secreted by stem cells, the reviewers decided to exclude these studies to ensure

the analysis remained focused and precise. The reasons for any final decisions to exclude certain studies were documented in detail. The reasons were recorded alongside the study's title in the Rayyan web-based application, and keywords were used to help categorize or/and clarify the decisions made. In cases where consensus could not be reached, the matter was discussed with the correspondence author (VR), who made the final decision. Papers that satisfied the required eligibility criteria were selected.

DPN parameters and outcomes

The clinical diagnosis of DPN is confirmed by assessing signs and symptoms, as well as measuring reduced functional parameters such as motor and sensory nerve conduction velocity (MNCV and SNCV) and the vibration perception threshold (VPT) [19, 20]. The VPT specifically evaluates the ability to sense vibrations in functional myelinated nerve fibers. The voltage measured was greater than 16 V, indicating a diagnosis of DPN [21–23]. The Toronto Clinical Scoring System (TCSS) is a straightforward and precise tool used to assess diabetic neuropathy. A score of <5 indicates the absence of neuropathy, whereas a value of >5 is interpreted as neuropathy. A score of 6–8 suggests mild neuropathy, 9–11 indicates moderate neuropathy, and 12–19 indicates severe neuropathy [24–30].

Hence, the main focus was to assess the efficacy and safety of stem cell treatments for managing DPN by analyzing the results of these specific measures. More precisely, the functional parameters consisted of MNCV and SNCV (m/s), VPT (V), and TCSS. The secondary outcome examined the correlation between age, the specific type of stem cell used, the duration of follow-up, and the efficacy and safety of stem cell therapy.

Data extraction and quality assessment

The manuscript's data extraction process involved putting all the data into a pre-established data extraction form by two separate authors (SJ and SDA). As mentioned above, the data extraction variables can be found in the "DPN parameters and outcomes" part of this work. Each author's data was cross-checked by the other to ensure accuracy, and any discrepancies were addressed through discussions and a thorough review of the full-text papers. Each author explained how they interpreted the data and arrived at their respective values. For example, the authors encountered several differences, notably the inclusion of VEGF and CD73 factors, as well as other variables such as SNL (ms) and NTSS-6 Score. After consulting with each other and reviewing relevant literature, the authors reached a consensus to exclude these factors from the data extraction sheet due to their limited use across the majority of studies. Numerical and unclear errors, arising from ambiguous definitions of the results, were addressed by precisely re-evaluating the full texts. If disagreements persisted, they were resolved either through further debate or by the correspondence author (VR), who made the final decision. VR evaluated the disputed items based on the full texts of the articles and the arguments presented by both reviewers. Based on the discussions and the input from the third reviewer, decisions are made regarding which values to retain in the final dataset. The corresponding author was contacted to get further data in cases where there was missing data or when the necessary information from each included study was ambiguous or inaccurate. Two reviewers (SJ and SDA) independently assessed the risk of bias in all the papers included. They utilized the risk of bias in non-randomized studies—of interventions (ROBINS-I) assessment tool [31] and the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [32].

Statistical analysis

The statistical analyses were performed with STATA version 14 (Stata Corp., College Station, TX). The results of the meta-analysis were presented as the weighted mean differences (WMD) along with a 95% confidence interval. An effect size combination using a random-effects model was conducted. The assessment of inter-study heterogeneity was conducted using the Q and I^2 statistics. In every analysis, if the value of I^2 exceeded 50% or the p-value was less than 0.1, the data was deemed to be heterogeneous. In addition, subgroup and sensitivity analyses were carried out to assess the origin of heterogeneity and the influence on the overall effect size by eliminating particular studies, respectively. The funnel plot, Begg's test, and Egger's test were employed to evaluate the presence of potential publishing biases in the research.

Results

Out of the 5431 entries collected after the initial review, 2479 remained after deduplication. After conducting a thorough examination and excluding certain manuscripts, 15 studies were found to be eligible for a comprehensive evaluation. Seven studies [33–39] satisfied the final inclusion criteria and were selected for both qualitative and quantitative analysis (Fig. 1).

All of these investigations were carried out exclusively in China and involved patients diagnosed with DM-2, except for one study conducted in Egypt, which included patients diagnosed with both DM-1 and DM-2 [37]. An examination was performed on a sample of 400 patients, with a male-to-female ratio of 1.3:1. The mean ± standard deviation age of the 345 patients was 62.4 ± 8.5 years. Five

studies utilized the bone marrow-derived mononuclear cell (BMMNC) [34, 35, 37–39], while the umbilical cord-derived mesenchymal stem cell (UCMSC) was employed in the remaining two trials [33, 36]. All of the studies utilized intramuscular transplantation as the method, except one study that employed intravenous transplantation of stem cells. All the particulars of the studies are displayed in Table 1. The assessment of bias in the included research indicated that three studies had a low risk of bias [35, 37, 38], while the other four studies raised some concerns [33, 34, 36, 39]. All non-randomized trials were detected as low risk of bias in the classification of interventions bias. Additionally, half of the non-randomized trials showed a low risk of bias in the measurement of outcomes and selection of reported results. A low risk of bias was detected for deviations from intended interventions and missing data in 2 out of 6 studies, while 1 study showed a moderate risk of bias, and 3 studies provided no information. For confounding bias, 2 out of 6 studies had a low risk, while 4 studies lacked sufficient information. The randomized trial showed concerns related to the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Table S2 provides detailed information about the bias assessment process. Four factors, namely MNCV, SNCV, VPT, and TCSS, were utilized for meta-analysis and are individually shown below.

Meta-analysis, sensitivity analysis, and meta-regression

The meta-analysis showed that stem cell transplantation led to significant improvements in MNCV and SNCV factors in patients. The MNCV factor had a z-score of 7.2 with an improvement of 2.2 (95% CI 1.6, 2.8), while the SNCV factor had a z-score of 4.6 with an improvement of 1.9 (95% CI 1.1, 2.6). The VPT and TCSS both significantly decreased, with a decrease of − 2.9 (95% CI − 4.0, − 1.8) and − 3.6 (95% CI − 5.0, − 2.2), respectively, as indicated by z-scores of − 5.2 and − 5.1, respectively (Figs. 2, 3, 4). Sensitivity analysis aims to evaluate the resilience of the overall findings by systematically removing each study and its influence on the cumulative effect size. The sensitivity analysis indicated that after excluding

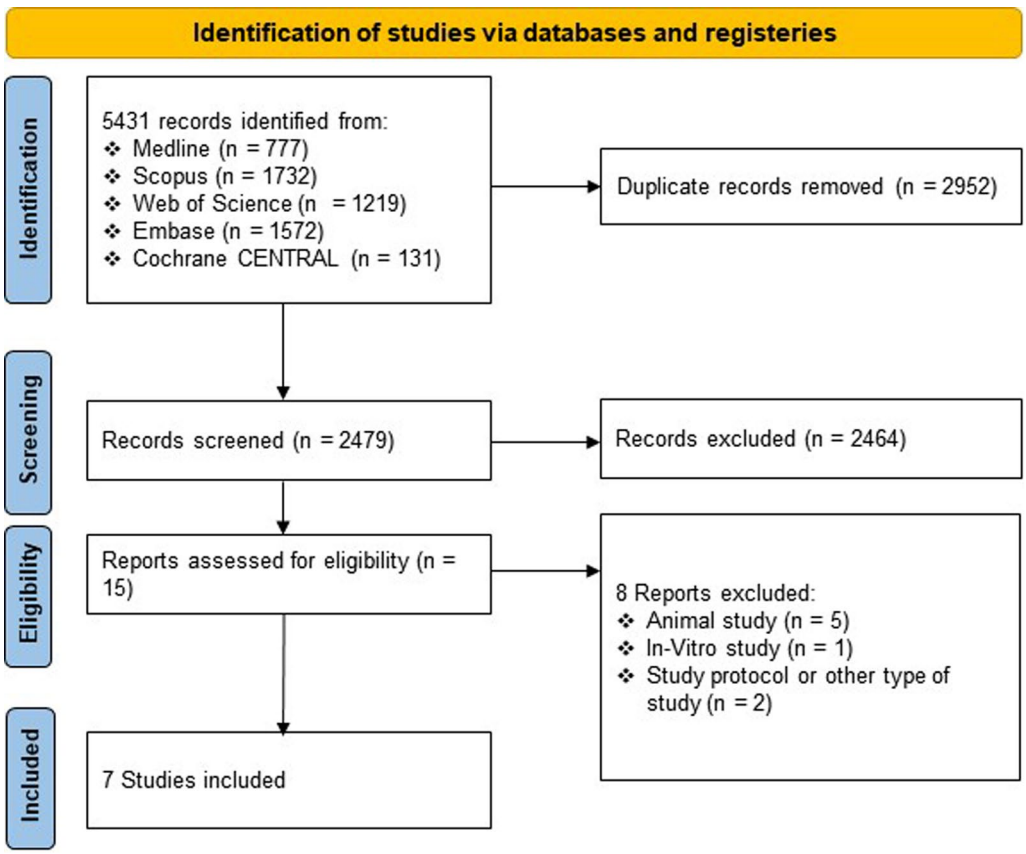

Fig. 1 Flow diagram of the PRISMA 2020 guidelines for systematic review and meta-analysis of stem cell therapy for individuals with diabetic peripheral neuropathy

Table 1 The characteristics of the included studies, such as demographics, stem cell types, analyses performed, and features of complications

Studies	Country	Population, No	Sex (male), No. (%)	Age (year), mean ± SD, or range	Duration of DM (year)	Stem cells			Analyzed neuron	Time of analysis (MPT)	Complication
						Type	Transplantation method	Dosage			
Mao et al. [38]	China	168	95	63·7 ± 8·8	10·7 ± 5·3	BMMNC	IM	NA	Posterior tibial, peroneal, sural, and superficial peroneal nerves	3 and 12	19 patients experienced slight pain or swelling feelings at the injection sites several hours after the transplantation, which disappeared in three days
Riad et al. [37]	Egypt	10	6	41·2 ± 4·6	NA	BMMNC	IV	NA	Tibial, sural, ulnar, and common peroneal nerves	3	NA
Wang et al. [39]	China	83	49	66·0 ± 10·2	12·0 ± 5·4	BMMNC	IM	$2·0 \pm 0·5 \times 10^8$ per leg	Tibial and peroneal nerves	3 and 6	Some patients felt swelling and heat in the transplanted lower limb, accompanied by pain relief
Wang et al. [36]	China	32	19	71–81	17·0 ± 5·4	UCMSC	IM	$5·0 \pm 1·4 \times 10^8$ per leg	Tibial and peroneal nerves	3 and 6	Some patients felt swelling and heat in the transplanted lower limb, accompanied by pain relief
Wei et al. [35]	China	60	31	59·3 ± 5·6	9·8 ± 5·1	BMMNC	IM	NA	Posterior tibial, peroneal, sural, and superficial peroneal nerves	3 and 12	Three patients experienced slight pain at the injection sites 2 h after transplantation
Zhang et al. [34]	China	24	16	56·8 ± 6·1	NA	BMMNC	IM	$1·1 \times 10^{12}$/L	Tibial and common peroneal nerves	3	After 3 months, the limb pain, numbness, cold sensation, intermittent claudication, and rest pain of patients all improved
Zhu et al. [33]	China	23	12	69–84	23·0 ± 5·4	UCMSC	IM	$1·2 \times 10^8$–$1·1 \times 10^9$ per leg	Tibial and peroneal nerves	3 and 6	Some patients felt swelling and heat in the transplanted lower limb, accompanied by pain relief

BMMNC human bone marrow mononuclear cells, *DM* diabetes mellitus, *IM* intramuscular, *IV* intravenous, *MPT* months post transplantation, *NA* not accessible, *SD* standard deviation, *UCMSC* human umbilical cord-derived mesenchymal stem cells

certain studies, the WMD were as follows: for MNCV, excluding Wei et al. [35], it was 2.4 (95% CI 1.9, 2.8); for SNCV, excluding Wang et al. [39], it was 2.0 (95% CI 1.2, 2.8); for VPT, excluding Wang et al. [36], it was − 3.1 (95% CI − 4.3, − 1.9); and for TCSS, excluding Wei et al. [35], it was − 4.1 (95% CI − 5.3, − 2.9). During the publication bias and heterogeneity of the study, none of the variables exhibited any signs of publishing bias. Additionally, the variables MNCV and VPT demonstrated homogeneity. Table 2 provides a comprehensive overview of the publishing bias and heterogeneity, whereas Fig. 5 displays the funnel plot of all variables.

A meta-regression analysis was performed to demonstrate the impact of patients' age and follow-up duration on MNCV, SNCV, and VPT after stem cell transplantation. The TCSS analysis was deemed invalid owing to insufficient data. The meta-regression analyses of all variables were not statistically significant. The results of meta-regressions are presented in Table 3, and meta-regression plots of all factors are presented in Figs. S1–S6.

Subgroup analysis

The BMMNC and UCMSC were utilized in this investigation, and as a result, subgroup analysis was performed. However, it is worth noting that all of the studies that reported the TCSS used BMMNC, thus rendering subgroup analysis unnecessary for the TCSS. The MNCV in the UCMSC group had superior outcomes, whereas

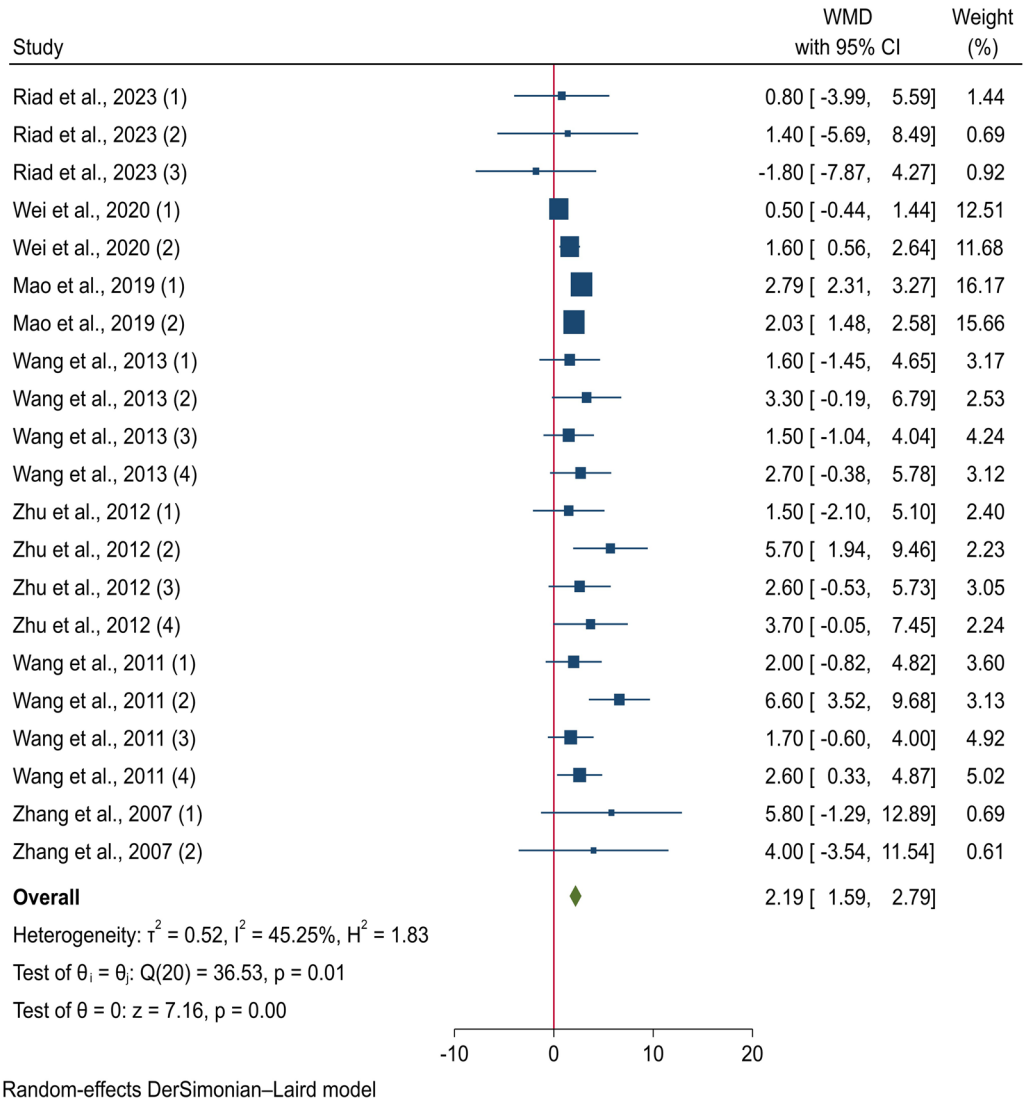

Fig. 2 Meta-analysis of motor nerve conduction velocity in stem cell therapy for individuals with diabetic peripheral neuropathy

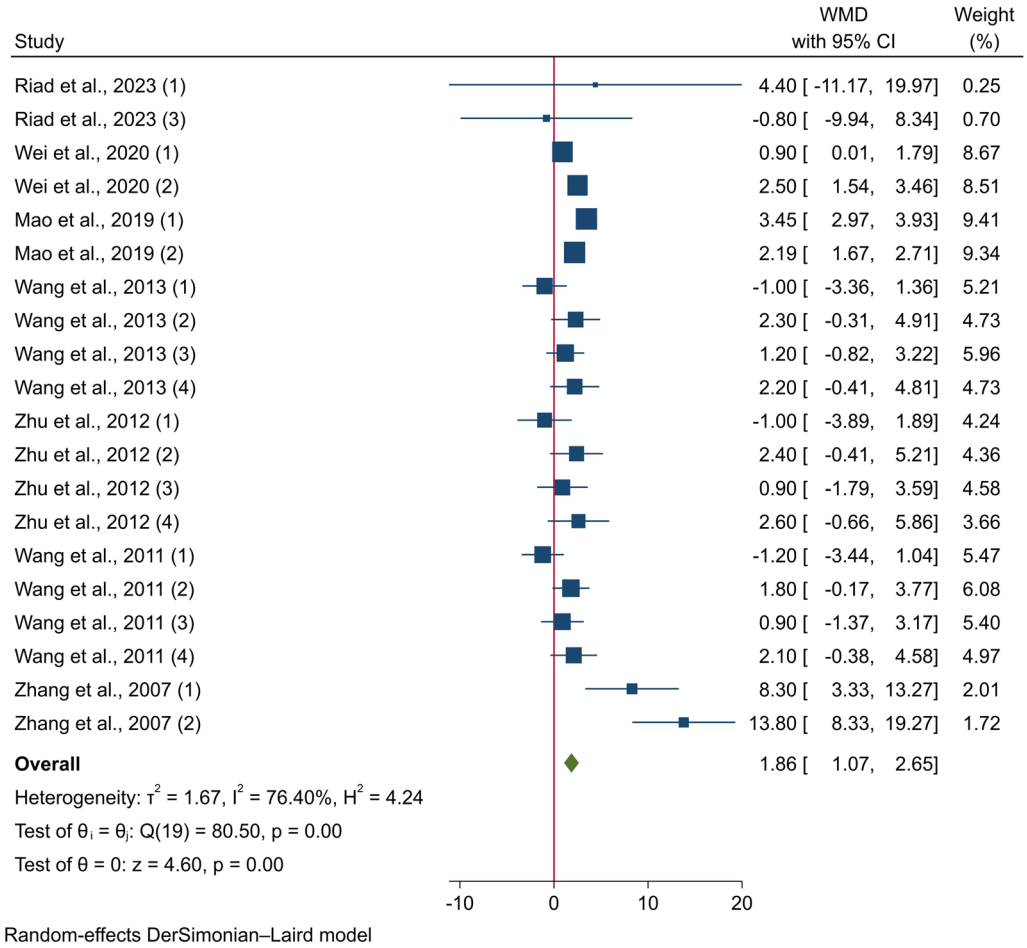

Fig. 3 Meta-analysis of sensory nerve conduction velocity in stem cell therapy for individuals with diabetic peripheral neuropathy

the SNCV and VPT demonstrated greater enhancement in those who received BMMNC. All of the parameters evaluated in the subgroup analysis were homogenous except for MNCV and SNCV in the BMMNC group. The specific findings of the subgroup analysis are displayed in Table 4.

Discussion

DPN, a prevalent condition among diabetic patients, significantly burdens both patients and the health care system due to the lack of a known, highly effective treatment. We conducted a systematic review and meta-analysis on the use of stem cells as a promising new treatment for DPN. The results of the collected studies indicated that only two types of stem cells were used in clinical trials: BMMNC and UCMSC. Overall, our study showed a significant improvement in nerve conduction velocity following stem cell transplantation in DPN patients.

Mesenchymal stromal cells (MSCs) are frequently used in cell therapy studies and are found in various tissues, including the umbilical cord (UC), dental pulp (DP), and placenta [40–42]. These multipotent cells can differentiate into several tissues, including bone, cartilage, and adipose tissue [43].

MSCs initiate rolling along the endothelium via CD44, with potential involvement of selectins like P-selectin, mediated by ligands such as galectin-1 or CD24. Chemokines like CXCL12 and MCP-1 increase the affinity of integrins on MSCs, leading to firm adhesion and arrest on the endothelial cells, primarily through CD49d (α4β1) binding to VCAM-1. MSCs secrete matrix metalloproteinases (MMPs) to traverse the endothelial basement membrane and migrate towards injury sites guided by chemotactic signals such as PDGFα, CXCL12, and other chemokines. Chemokine signaling, particularly through the CXCR4 receptor and its ligand SDF-1/CXCL12, plays a crucial role in regulating stem cell migration during development and in various diseases [44, 45]. TGF-β3 and TNF-α both facilitate migration [46, 47]. CD44 fucosylation on MSCs can enhance homing

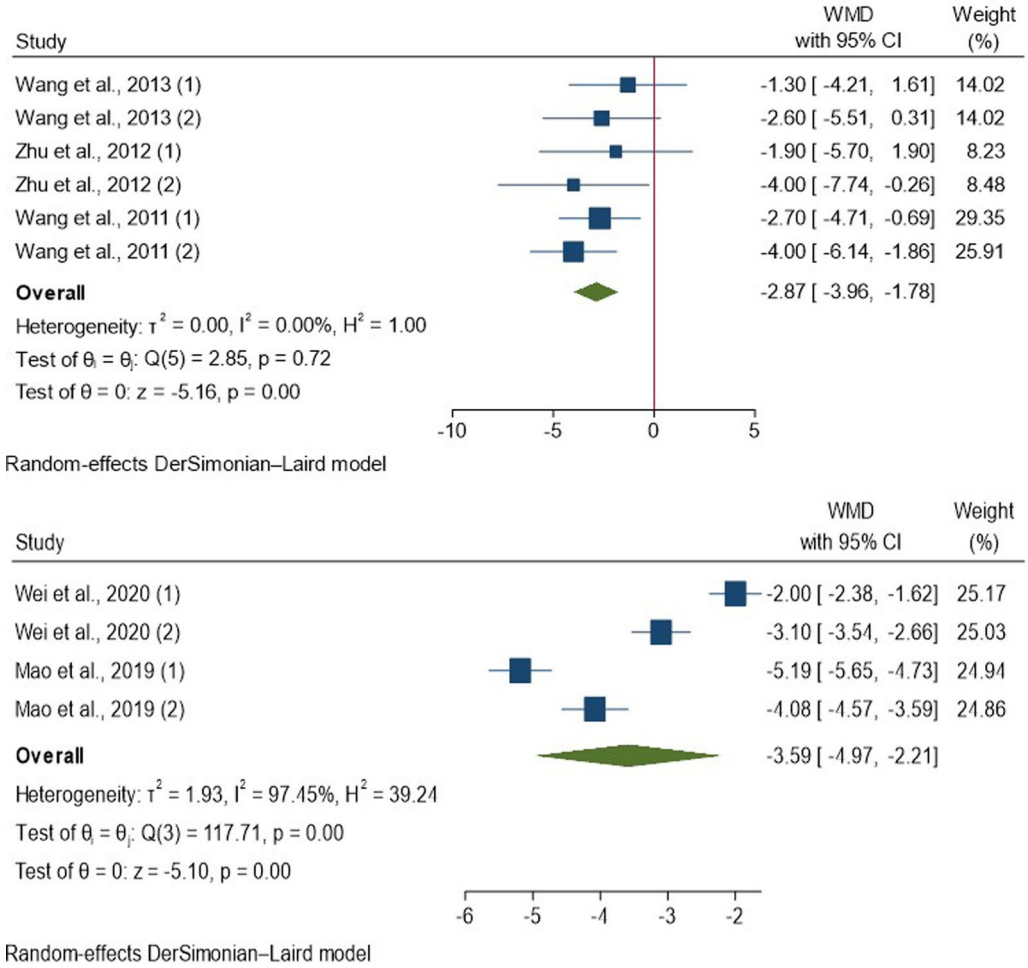

Fig. 4 Meta-analysis of stem cell therapy effects in individuals with diabetic peripheral neuropathy: vibration perception threshold (top) and Toronto clinical scoring system (bottom)

Table 2 Details of heterogeneity and publication bias assessment for all variables based on Egger's and Begg's tests

Variables	Heterogeneity				Publication bias		
	I^2 Statistics (%)	Q statistics	τ^2	*P*	Coef	*P*	Kτ
MNCV (m/s)	45·25	36·53	0·52	0·010	0·44	0·292	42
SNCV (m/s)	76·40	80·50	1·67	< 0·001	0·64	0·267	50
VPT (V)	0	2·85	0	0·720	0·82	0·656	2
TCSS	97·45	117·71	1·93	< 0·001	−47·86	0·160	−4

Kτ Kendall rank correlation coefficient, *MNCV* motor nerve conduction velocity, *P* p-value, *SNCV* sensory nerve conduction velocity, *TCSS* Toronto Clinical Scoring System, *VPT* vibration perception threshold, *τ2* tau-squared, *χ2* chi-squared

through the regulation of key signaling molecules such as CXCL12 and sphingosine-1-phosphate (S1P) [48]. Cellular signaling pathways involved in MSC migration and homing include the CXCR4/CXCL12 axis, which is enhanced by rapamycin pre-conditioning, and the PI3K-Akt, MAPK, and Jak/Stat pathways, which facilitate cell passage through changes in focal adhesion kinase (FAK) and the cytoskeleton in response to CXCL12 [49, 50]. Differences in homing capabilities can arise from variations in tissue type and MSC properties [51]. After homing, MSCs secrete cytokines and extracellular vesicles, enhancing the functionality of both local and distal tissues and improving organ function [52]. García-Sánchez et al. have discussed strategies to enhance

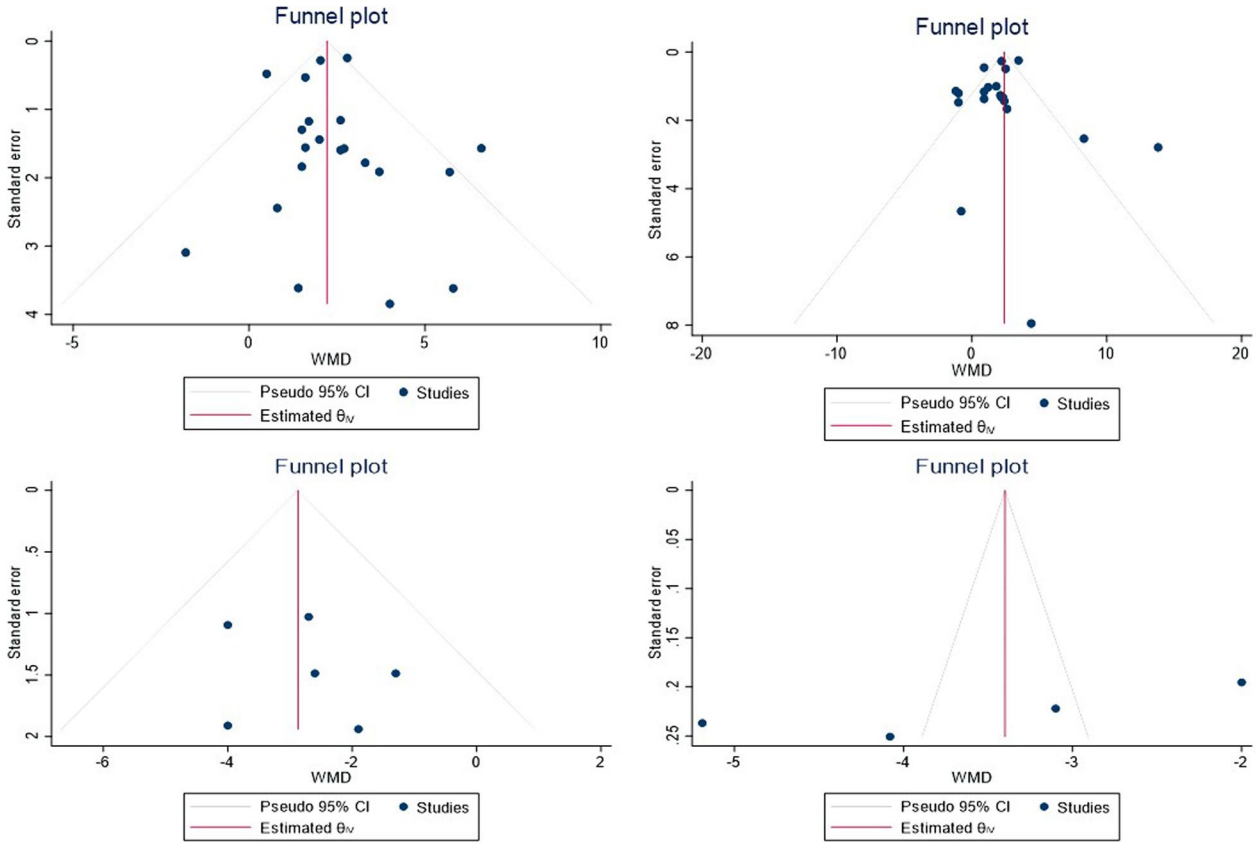

Fig. 5 Funnel plots illustrating potential publication bias for different outcomes: motor nerve conduction velocity (top left), sensory nerve conduction velocity (top right), vibration perception threshold (bottom left), and Toronto clinical scoring system (bottom right)

Table 3 Meta-regression based on the age of patients and follow-up period used in therapy for individuals with diabetic peripheral neuropathy

Groups	Factor *	No	Coef. (95% CI)	P	I^2 statistics (%)	τ^2
Age	MNCV (m/s)	21	0·07 (−0·01, 0·16)	0·072	36·04	0·34
	SNCV (m/s)	20	−0·10, (−0·22, 0·01)	0·069	76·17	1·63
	VPT (V)	6	0·09 (−0·21, 0·40)	0·440	0	0
Follow-up period	MNCV (m/s)	21	−0·002 (−0·19, 0·19)	0·981	46·32	0·80
	SNCV (m/s)	20	0·08 (−0·20, 0·36)	0·573	74·64	2·12
	VPT (V)	6	−0·47 (−1·50, 0·56)	0·276	0	0

MNCV motor nerve conduction velocity, *P* p-value, *SNCV* sensory nerve conduction velocity, *VPT* vibration perception threshold, τ^2 tau-squared

*The meta-egression did not conduct on Toronto clinical scoring system due insufficient data

the engraftment and survival of MSCs in therapeutic applications. Culture conditions such as serum presence, oxygenation, glucose level, and harsh environment during implantation can impact MSC survival [53, 54]. Replicative senescence in MSCs is characterized by a short lifespan in culture, primarily due to telomere shortening and oxidative stress. Interventions like vitamin E treatment can counter oxidative stress [55]. To enhance in vitro culture conditions and prevent senescence, several techniques can be employed. These include using senolytic drugs to selectively target senescent cells, modifying culture media to incorporate factors that support telomere stability, and utilizing xeno-free culture conditions. MSCs naturally exist in low-oxygen environments, while they are typically cultured in higher oxygen levels in vitro. Preconditioning MSCs with low oxygen or pharmacological agents that mimic their natural environments improves their survival

Table 4 Subgroup analysis based on the type of stem cell used in therapy for individuals with diabetic peripheral neuropathy

Subgroups	Factors *	Study No	WMD (95% CI)	Heterogeneity			
				I^2 statistics (%)	Q statistics	τ^2	*P*
BMMNC	MNCV (m/s)	13	2·07 (1·32, 2·82)	61·84	31·45	0·69	0·002
	SNCV (m/s)	12	2·28 (1·28, 3·29)	82·80	63·95	1·70	< 0·001
	VPT (V)	2	− 3·31 (− 4·78, − 1·84)	0	0·75	0	0·386
UCMSC	MNCV (m/s)	8	2·60 (1·47, 3·74)	0	4·60	0	0·709
	SNCV (m/s)	8	1·12 (0·12, 2·12)	14·89	8·22	0·31	0·313
	VPT (V)	4	− 2·33 (− 3·96, − 0·70)	0	1·33	0	0·723

BMMNC bone marrow mononuclear cells, *Kτ* Kendall rank correlation coefficient, *MNCV* motor nerve conduction velocity, *P* p-value, *SNCV* sensory nerve conduction velocity, *UCMSC* Umbilical cord mesenchymal stem cells, *VPT* vibration perception threshold, *WMD (95% CI)* weighted mean differences (95% confidence interval), τ^2 tau-squared

*All of the studies that assessed Toronto clinical scoring system was used bone marrow mononuclear cells, therefore, the subgroup analysis did not conduct for Toronto clinical scoring system

and regenerative capacity in hypoxic conditions after transplantation. This technique also reduces the risk of malignant transformation. Culturing MSCs in 3D structures (spheroids) enhances their survival, increases the expression of beneficial factors like angiogenic genes, and improves their therapeutic effectiveness. Various delivery routes, including local, systemic, and scaffolds, have different implications for MSC retention and efficacy. Biocompatible scaffolds can improve MSC viability and facilitate engraftment by mimicking the extracellular matrix (ECM) environment. MSCs' homing process can be enhanced through preconditioning and signaling pathways mainly the SDF-1/CXCR4 axis. Avoiding anoikis, a form of cell death caused by the loss of ECM interaction is another challenge. Encapsulating MSCs in hydrogels or using integrin-specific biomaterials helps maintain cell adhesion and boosts survival. Techniques to manipulate integrins, important for cell adhesion, have also been shown to improve MSC survival and homing in animal models [55].

Previous studies indicated that MSCs can have neuroprotective effects in animal models of Parkinson's disease [56]. Furthermore, through secreting anti-inflammatory, anti-apoptotic molecules, and trophic agents like fibroblast growth factor (FGF), vascular endothelial growth factor A (VEGFA), and nerve growth factor (NGF), they show nerve regeneration, angiogenesis, and protection against apoptosis [57, 58]. Animal studies regarding the usage of MSCs in DM demonstrated that glycemic status in diabetic mice is improved through regenerating pancreatic beta cells. Additionally, MSC transplantation could decrease the rates of thermal hyperalgesia and mechanical allodynia in mice with neuropathy [59, 60]. Furthermore, Pan et al. showed how MSC transplantation could improve DPN symptoms through nerve myelin lesions and nerve regeneration. He also indicated that MSCs could activate Schwann cells, probably through regulation of the Wnt signaling cascade and apoptosis inhibition [61].

In recent years, there has been growing interest in extracellular vesicles like exosomes and microvesicles derived from stem cells, recognized as potential diagnostic indicators with significant contributors to therapeutic effects [62, 63]. Most cell types generate extracellular vesicles. Extracellular vesicles play a pivotal role in facilitating intercellular communication. Research has demonstrated that extracellular vesicles have significant therapeutic promise by transferring their contents into recipient cells and modulating various signaling cascades [64]. These vesicles are small, membrane-bound particles that cells release, and they carry bioactive molecules such as proteins, mRNAs, microRNAs, and lipids [65–67]. Recent studies have demonstrated that extracellular vesicles released by stem cells and immune cells can influence gene expression in recipient cells, offering a promising approach for treating diabetes and its complications [68]. Exosomes carry specific miRNAs that regulate key processes like neural inflammation, oxidative stress, and cell death, all linked to DPN. It suggests that exosomes and their mRNA can be useful biomarkers for diagnosing and monitoring the progression of DPN. However, further research on exosomal signaling pathways is essential, as they hold significant potential for revealing disease mechanisms and developing innovative therapeutic strategies [69, 70]. Studies have highlighted that MSC-derived exosomes (MSC-exos) can be applied to address various aspects of diabetes and its microvascular complications, such as enhancing pancreatic beta cell function, improving insulin sensitivity, and treating diabetic neuropathy [71, 72].

In a study involving diabetic mouse models, MSC-exos significantly enhanced motor and sensory nerve

conduction velocities and improved mechanical and thermal sensitivities, indicating enhanced neurological outcomes. MSC-exosomes improved blood flow and microvascular density in sciatic nerves and plantar skin, and increased PGP9.5+ intraepidermal nerve fiber density. They enhanced axonal health by increasing the density and diameter of myelinated nerve fibers and improving myelin thickness. MSC-exosomes suppressed the accumulation of activated macrophages (CD68+) and reduced pro-inflammatory cytokines (TNF-α, IL-1β) in sciatic nerve tissues and circulation. The research has emphasized the important role of macrophages as key regulators of neuroinflammation, showing how they contribute to inflammation and subsequent cellular damage. Ultimately, these processes can lead to nerve dysfunction or death, resulting in clinical neuropathy [73]. Additionally, these mice exhibited lower levels of inflammatory cytokines, attributed to the action of specific miRNAs (miR-17, miR-23a, and miR-125b) that suppressed the TLR4/NF-κB signaling pathway. This suppression leads to decreased neuronal dysfunction, suggesting a mechanism explaining the exosomes' therapeutic benefits [74].

Another similar study with diabetic mouse models used MSC-exos enriched with miR-146a, showing potential for improving clinical outcomes in diabetic peripheral neuropathy via the same pathway. The study found that mice treated with exo-146a exhibited significant increases in nerve conduction velocity and reduced sensitivity to thermal and mechanical stimuli. Exo-146a treatment enhanced neurovascular function by increasing nerve fiber density and blood flow, reduced inflammatory monocytes and activated macrophages while promoting M2 polarization, and decreased adhesion molecule expression in endothelial cells, inhibiting inflammatory signaling pathways [75]. In a rat model of DPN, Singh et al. showed that combining BMSCs exosomes with polypyrrole nanoparticles (PpyNps) treatment significantly improved MNCV and compound muscle action potential (CMAP), indicating enhanced nerve regeneration. The exosomes enhanced nerve regeneration, protecting against oxidative stress, supported muscle recovery, improved systemic organ health, and modulated gene expression related to nerve repair in a diabetic peripheral neuropathy model [76].

The BMMNC therapies are among the most widely accepted therapies for different acute and chronic conditions. A unique advantage of using these cells is that they can be obtained from a patient's bone marrow and then reinfused into the same patient; this reduces the chance of rejection [77–79]. Animal studies have shown the beneficial properties of BMMNCs in DPN. BMMNCs have improved neovascularization, probably through increasing secretion of angiogenic factors including VEGFA, FGF2, and angiopoietin-1 [80, 81]. The medical literature shows a promising role for BMMNC transplantation in ischemic diseases [80]. This has increased the interest of scientists in employing a comparable approach for treating DPN patients [82]. A recent animal study demonstrated that injecting peripheral blood mononuclear cells (PBMCs) in DPN could result in partial blood flow recovery and improved MNCV of the sciatic nerve [83, 84]. Shibata et al. reported that using BMMNCs in STZ-induced diabetic rats could improve nerve conduction velocity, boost the concentration of small blood vessels in the muscle, improve blood flow, and improve blood flow [58]. Kondo et al. reported that there is a difference in efficacy of BMMNCs derived from young rats compared with mature or diabetic rats [85, 86].

Our meta-analysis demonstrated a significant improvement in MNCV and SNCV following stem cell transplantation, highlighting the positive impact of cell therapy on nerve function. Moreover, a reduction in VPT and TCSS after cell therapy suggests improvements in sensory and overall neuropathy symptoms.

We hypothesize that these results could be due to the angiogenic properties of these cells, as they can improve blood flow to the affected site and improve nerve function. Also, neurotropic factor secretion from these cells, including brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), and NGF, could help nerve regeneration and DPN symptoms.

Our meta-analysis subgroup analysis indicated that SNCV and VPT had greater enhancement in those who received BMMNC compared to UCMSC. Also, MNCV in the UCMSC group had superior outcomes compared to other groups. We have proposed the following hypothesis to explain this outcome: UCMSCs may have higher proliferation and differentiation properties in motor neurons, while such characteristics are higher in BMMNCs differentiation in sensory neurons. For instance, UCMSCs may secrete higher levels of neurotropic factors such as NGF, BDNF, and GDNF in motor neurons than BMMNCs, or they may have a higher angiogenic potential compared to BMMNCs. This could lead to improved blood flow and oxygenation to the affected nerves, thereby improving nerve function. Furthermore, we can hypothesize that UCMSCs have better specific immunomodulatory properties compared to BMMNCs in motor neuron regeneration, which could lead to inflammation reduction and result in a more favorable microenvironment for nerve regeneration and repair.

Lastly, UCMSCs may have a higher survival rate and engraftment potential in motor neurons compared to BMMNCs, which could lead to more cells persisting in

the target tissue and contributing to the observed superior outcomes.

Despite the fact that swelling and heat in the transplanted lower limb, along with pain relief, were the most commonly reported side effects in patients, it is crucial to address several concerns in subsequent studies. While stem cell therapy shows promise in treating DPN by promoting nerve regeneration and improving patient outcomes challenges such as tumorigenicity, immune rejection, optimizing treatment protocols, refining delivery methods, and ensuring long-term safety and outcomes remain to be addressed for its full potential to be realized [1, 70, 87, 88]. Additionally, regulatory constraints and the need to make the therapy available and affordable for regular people present further obstacles.

First, we should consider the risk of tumor development, as seen in murine MSCs in vitro [89] and after allogeneic transplantation of MSCs [90]. The included studies did not have long-term follow-up, and future studies should investigate the long-term side effects of cell therapy, including malignancies [91]. Undifferentiated or transformed cells could potentially form tumors [92, 93]. Stem cells' ability to self-renew can lead to uncontrolled growth, as seen with undifferentiated pluripotent stem cells (PSCs) that can form teratomas if not fully differentiated [94, 95]. MSCs are generally safer but are not completely free from tumorigenic risks, as seen in a case where a patient developed glioproliferative lesions after receiving MSCs [96].

Various methods have been developed to eliminate the undifferentiated cells while preserving the viability of differentiated cells such as PluriSIn, mitochondrial dyes, and doxorubicin [97–100]. Concerns about tumorigenicity arise during and after therapy. Assessing tumorigenicity is crucial to ensure the safety of stem cell therapies. There are numerous methods for tumorigenicity assessment such as animal models, PCR methods, and flow cytometry. Each method has trade-offs. Animal models that serve as gold standard assays take too long, while PCR and flow cytometry rely heavily on specific biomarkers, which may not be universally reliable. There are major challenges in clinical practice including establishing sensitivity levels that are relevant to clinical practice, identifying the minimum number of rare cells required to form tumors, and performing thorough validation with real-world samples. Potential hazards such as residual undifferentiated stem cells and cell transformations must be controlled. Rigorous quality control is necessary to ensure the safety of stem cell therapy. It's crucial to assess the risk of tumor formation, particularly when it cannot be avoided, and weigh it against the potential benefits of the therapy. Appropriate strategies to reduce or manage this risk should be implemented [92].

Risks not related to the product itself, such as those associated with immunosuppressive drugs and patient-specific factors, also need consideration. Immunosuppressants can reduce immune surveillance and increase tumor risks. Data-driven guidelines for the duration and use of these drugs are important, as is understanding individual patient risks, particularly those with cancer histories. Initial clinical data may be limited, so regulatory guidelines emphasize genetic testing to determine the cause of any observed tumors. Ongoing, long-term monitoring and patient registries are essential for confirming the safety of stem cell therapy. Therefore, due to the challenges and the lack of a unified standard for evaluating tumorigenicity, it is advisable to assess the risk of each cell therapy product on an individual basis [92, 95].

Another point to discuss is graft rejection, which is a significant concern, particularly in allogeneic transplantation. As we previously mentioned, BMMNC transplantation showed promising results, and future studies could delve further into the anti-rejection properties of these cells. The risk of immunological rejection is higher with donor-derived MSC treatment compared to self-derived therapy, which carries no such risk. However, allogeneic MSC therapy provides several advantages over autologous MSC therapy, including better scalability, lower production costs, and quicker availability for acute conditions. It also demonstrates enhanced biological functionality, despite the minimal risk of immune rejection. There is ongoing debate regarding the use of MSCs from donors with genetic predispositions to certain diseases, as these cells could potentially have long-term adverse effects on recipients. MSCs interact with their environment and may be influenced by both pathological and physiological factors, potentially affecting their behavior and efficacy. The variability among MSCs from different donors and their interaction with their microenvironment introduces uncertainties in their clinical application [101, 102].

For DPN stem cell therapy, it is important to identify the best timing, dose, and type of stem cells to use, as the progression of DPN through different stages can vary significantly from one patient to another. This variability means that a one-size-fits-all approach may not be effective. Refining treatment approaches is essential to fully harness the advantages of stem cell therapy, particularly concerning the route of administration with accurate equipment, to ensure that stem cells effectively reach the damaged nerves. Finally, it is essential to continuously evaluate the safety and effectiveness of stem cell therapy to track the persistence and integration of transplanted cells by employing thorough assessment techniques, including neurological examinations, motor and sensory testing, nerve conduction studies, biopsies,

novel molecular and imaging techniques, and patient-reported outcomes (PROs), to track patient progress over time [1, 70, 103, 104].

In summary, DPN is a persistent and long-term complication characterized by sensory and motor symptoms that can lead to significant morbidity and lower quality of life [105]. Stem cell therapy addresses the condition's root cause by promoting nerve regeneration and recovery. Unlike treatments like pharmacological interventions that only manage neuropathic symptoms, this approach has the potential to slow or even reverse the disease's development. As a result, patients may experience improvements in their symptoms and overall quality of life [24, 70].

It is important to mention that our systematic review and meta-analysis face a major limitation: a lack of high-quality, standard-controlled trials with a large sample size. Further, there were no clinical trials with long-term follow-up to assess the future complications of patients and the safety of this method. More studies will be needed to focus on conducting such studies to further our understanding of stem cell therapy as a novel treatment approach for DPN patients.

Conclusion

In conclusion, DM is a chronic metabolic disorder that can get further complicated by DPN. There is no standard, high-efficacy therapy for this complication. Clinical trials using stem cell therapy, though few, show promising results. Further studies should focus on examining the efficacy and effects of using different types of cell therapy in a large sample of patients with long-term follow-ups.

Supplementary Information

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Additional file 1.

Additional file 2.

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The authors declare that they have not used AI-generated work in this manuscript.

Author contributions
SA and SJ collaborated on several tasks, including title-abstract screening, data extraction, risk of bias assessment, drafting, and developing tables and figures. MR made valuable contributions by authoring the manuscript, conducting title-abstract screening, and extracting data. RT performed a thorough meta-analysis. RM performed a crucial role in formulating and implementing the search strategy, running electronic searches across several databases, while ZB tirelessly helped with analyzing titles and abstracts. AP, JH, MH, and ZG offered important constructive criticism throughout the entire research process. VR facilitated supervision, guaranteeing seamless communication and collaboration among the authors.

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
All gathered data was maintained in confidentiality and analyzed without any identifying names included. The study adhered to Helsinki's ethical principles. The Ethics Committee of Tehran University of Medical Sciences approved the study (Title of the approved project: Human Studies of the Efficacy and Safety of Stem Cells in the Treatment of Diabetic Peripheral Neuropathy: A Systematic Review and Meta-Analysis; Name of the institutional approval committee or unit: Research Ethics Committees of Sina Hospital; Approval number: IR.TUMS.SINAHOSPITAL.REC.1403.046; Date of approval: 2024-07-06).

Consent for publication
All authors have agreed to publish the paper in Stem Cell Research and Therapy (SCRT).

Competing interest
The authors declare that they have no competing interests.

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