Role of Regenerative Therapeutics in Diabetic Peripheral Neuropathy: Current Advances and Future Prospects

Sanjay Sharma1,2,* and Ravi Velamoor Rangarajan3

ABSTRACT

Diabetes is a chronic metabolic condition that has far-reaching consequences for human health. If there is no appropriate therapeutic treatment, diabetic peripheral neuropathy might lead to foot ulceration and limb amputation. Conventional pharmacological therapy has weak anti-DPN activity. By stimulating nerve regeneration, addressing the underlying causes of the disorder, and alleviating symptoms, stem cell therapy for diabetic peripheral neuropathy has the potential to alter the management of this debilitating illness. One of its most significant advantages is its ability to regenerate damaged nerves, as stem cells may differentiate into a variety of cell types, including neurons and supporting cells. Preclinical and early-phase clinical research has resulted in improvements in nerve conduction, pain alleviation, and sensory function in patients with diabetic peripheral neuropathy. Stem cell therapy can be tailored to each patient's specific ailment, ensuring personalized care that improves therapeutic outcomes. Future research may uncover further benefits and applications for stem cell treatment, such as refining stem cell source selection, experimenting with novel delivery systems, and capitalizing on tissue engineering advances. Combining stem cell therapy with gene editing or bioengineering procedures may improve regenerative potential in the treatment of diabetic peripheral neuropathy. To completely reap the benefits of stem cell therapy in diabetic peripheral neuropathy, obstacles must be overcome and treatment procedures must be improved. Stem cell therapy has the potential to revolutionize the treatment of diabetic peripheral neuropathy by encouraging nerve regeneration, and symptom relief. The present review discusses the noteworthy developments in various regenerative therapies for diabetic peripheral neuropathy.

Keywords: Conditioned medium, Diabetic peripheral neuropathy, regenerative medicine, stem cell therapy.

1. INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes, affecting approximately 50% of diabetic individuals. It results from damage to the peripheral nerves due to high blood sugar levels over an extended period (Fig.1). The condition typically presents as numbness, tingling, and pain, each symptom either occurring solely or in combination, predominantly in the lower extremities, but can also affect the arms and hands [1]–[3]. The symptoms may worsen at night, leading to difficulty sleeping. Patients may experience muscle weakness and a loss of reflexes as the disease progresses, increasing the risk of falls and injuries [4], [5]. DPN is a significant contributor to diabetic foot risk. According to a study [6], patients with DPN and sensory deficiencies have a seven-fold more significant likelihood of developing diabetic foot ulcers than those without these conditions. The loss of protective sensation and the lack of muscular coordination in the foot and leg that result from neuropathy raise the mechanical stress placed on the body during movement, which causes severe foot defects like claw toes or hammer toes and twisted ankles. It is challenging to treat diabetic foot; even if the ulcer heals, the recurrence rate is 30%–40% after a year [7], [8]. Thus, DPN can significantly impact the quality of life, impairing mobility and causing emotional distress.
Therefore, early diagnosis and management of diabetes are crucial to prevent or delay the onset of neuropathy. Traditional treatment options include maintaining good blood sugar control, managing symptoms with medications, physical therapy, and adopting a healthy lifestyle.

Current challenges in the management of diabetic peripheral neuropathy include the lack of definitive treatment options and the need for effective pain management strategies [9], [10]. Despite various treatment approaches, there is still no cure for this condition, and existing therapies mainly focus on symptom relief rather than addressing the underlying causes. Furthermore, it can be challenging to accurately diagnose diabetic peripheral neuropathy in some cases due to its asymptomatic nature [11]. Additionally, treatment compliance may be a challenge for patients, particularly with complex medication regimens and the need for lifestyle modifications [12]. Finding innovative and targeted therapies, improving early detection methods, and enhancing patient education are crucial for the effective management of diabetic peripheral neuropathy.

The rationale behind regenerative therapy in diabetic peripheral neuropathy lies in the potential to promote nerve regeneration and repair, addressing the underlying cause of the condition rather than merely managing symptoms. This approach aims to restore function and improve the quality of life for patients. Regenerative therapy utilizes various methods, such as stem cell transplantation, growth factor administration, and tissue engineering, to stimulate the repair and regeneration of damaged nerves. Stem cells can uniquely differentiate into various cell types, including nerve cells, and potentially replace damaged cells [13]. Growth factors promote neuronal growth, survival, and axonal regeneration [14]. Tissue engineering involves creating artificial nerve grafts or scaffolds to guide nerve regeneration [15]. By utilizing regenerative therapy, researchers hope to provide long-term benefits to patients with diabetic peripheral neuropathy, potentially reversing or slowing down the progression of the disease and offering a more effective treatment option.

2. Materials and Methods

Using the terms “diabetic peripheral neuropathy,” “regenerative therapy,” “stem cell therapy,” “mesenchymal stem cells,” and “pluripotent cells,” “umbilical cord derived stem cells”, a literature review was conducted using PubMed, Google Scholar, and Medline. Review articles, observational studies, randomized controlled trials, case series, case reports, and letters to the editor were among the types of publications in this collection. All sources with comparable information or evidence regarding the essential role of various types of stem cells in diabetic peripheral neuropathy were reviewed, gathered, and categorized. Major points for future study and practice were specified, and new evidence-based points were outlined.

3. Results

3.1. Mechanisms of Stem Cell Therapy in Diabetic Peripheral Neuropathy

There are several mechanisms through which stem cell therapy exerts its beneficial effects in DPN. These mechanisms can be broadly categorized into four main categories: paracrine effects, immunomodulation, angiogenesis, and differentiation.

3.1.1. Paracrine Effects

Stem cells can secrete various substances that can influence the microenvironment and promote tissue repair. This paracrine effect is mediated by the release of bioactive...
factors, growth factors, cytokines, chemokines, and extracellular vesicles, collectively referred to as the secretome. The secretome acts in paracrine to stimulate angiogenesis, which enhances blood flow to the damaged nerves and promotes neuroprotection by reducing inflammation and oxidative stress [16], [17]. Additionally, the secretome can modulate immune cell responses in the surrounding tissues and promote the survival and proliferation of resident cells, leading to nerve regeneration. Recent interest in vascular endothelial growth factor (VEGF) has been sparked by fresh findings on how it affects glia and neurons. Neurotrophic effects are encouraged by VEGF therapy in peripheral nervous system cells. For instance, VEGF increases the survival of both neurons and Schwann cells in the superior cervical ganglia and neural crest and encourages the proliferation and migration of Schwann cells. These VEGF-induced changes in survival and migration raise the possibility that it can prevent the loss of Schwann cells because of nerve damage and encourage the migration of newly generated Schwann cells to ensheath damaged nerve axons [18].

3.1.2. Immunomodulation

Chronic inflammation plays a significant role in the pathogenesis of DPN, contributing to nerve damage and dysfunction [19]. Stem cells possess immunomodulatory properties through the secretion of anti-inflammatory factors and the suppression of pro-inflammatory mediators [20], [21]. They can modulate the immune response by inhibiting the activation of immune cells, such as macrophages and T cells, and promoting the function of regulatory immune cells, such as regulatory T cells and M2 macrophages. This immunomodulatory effect helps reduce the nerves’ inflammatory response and promotes a pro-regenerative environment that supports nerve repair.

3.1.3. Differentiation

Stem cells can differentiate into various cell types, including neuronal cells and Schwann cells, which are vital for proper nerve function [22]. In the context of DPN, stem cells can potentially differentiate into neuronal progenitor cells and restore the damaged nerve fibers [23]. Additionally, stem cells can differentiate into Schwann-like cells, which promote nerve regeneration and provide a conducive environment for axon regrowth [24]. However, the extent of differentiation and incorporation into the nervous system after transplantation remains controversial due to understanding of the fate of these cells post-administration, especially through different delivery routes, including systemic administration via an intravenous (IV) route or tissue-specific administration, such as dorsal pancreatic administration. It is important to understand the distribution of these cells after injection to expand our understanding of the underlying mechanisms of action of treatments. Hence, the paracrine effects and immunomodulatory properties of stem cells appear to play more significant roles in promoting nerve repair.

3.1.4. Angiogenesis

Angiopoietin-2, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-1, and the extracellular matrix (ECM) environment all interact with one another to control the angiogenesis process. Furthermore, in the process of wound healing, sprouty2, pigment epithelium-derived factor (PEDF), low-density lipoprotein receptor-related protein (LRP)6, thrombospondin (TSP)1, chemokine (C-X-C motif) ligand (CXCL)10, chemokine (C-X-C motif) receptor (CXCR)3, heparin-binding EGF-like growth factor (HB-EGF), epidermal growth factor receptor (EGFR), semaphorin-3a, neuropilin-1, neural/glial antigen (NG)2, laminin-8, laminin-10, and regulator of G protein signalling (RGS)5 also regulate angiogenesis. By controlling the expression of the ECM receptor, v3, an integrin receptor for fibrin and fibronectin, ECM directly controls angiogenesis and vasculogenesis [25]–[27]. ECM production and angiogenesis are supported by cytokines released by fibroblasts and macrophages that have invaded the area. The mobilization of sprouting vasculature into fibrin and fibronectin-rich tissue caused by the expression of integrin receptors promotes wound healing. However, vessel development regresses and degenerates through apoptosis involving anti-angiogenic factors when granulation tissue and ECM are replaced by collagen-rich tissues [28].

3.2. Sources of Stem Cells

3.2.1. Mesenchymal Stem Cells (MSCs)

MSCs can self-renew and have the capacity to differentiate into a variety of cell types, including neurons, adipocytes, chondrocytes, and osteoblasts. Bone marrow, adipose tissue, neural tissue, amniotic fluid, umbilical cord, placenta, menstrual blood, and dental pulps can all be used to generate MSCs. Bone marrow-derived mesenchymal stem cells (BM-MSCs) have gained significant attention in diabetic neuropathy therapy [29], [30]. These cells possess regenerative and immunomodulatory properties, making them attractive candidates for treating nerve damage and dysfunction associated with diabetic peripheral neuropathy (DPN). BM-MSCs have been shown to differentiate into various cell types, including nerve cells and Schwann cells, promoting nerve regeneration. Moreover, they secrete a plethora of growth factors and cytokines that enhance angiogenesis, reduce inflammation, and create a favorable environment for tissue repair. Clinical studies have demonstrated promising results in terms of pain reduction, sensory improvement, and enhanced nerve function after BM-MSC therapy in DPN patients [31].

3.2.2. Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells (iPSCs) offer exciting potential for treating diabetic neuropathy [32]. iPSCs are derived by reprogramming adult cells, such as skin cells, into a pluripotent state, allowing them to differentiate into various cell types. This includes nerve cells and Schwann cells, making them a valuable resource for nerve repair and regeneration in diabetic neuropathy [33]. iPSCs can be generated from the patient’s own cells, reducing the risk of immune rejection. Although iPSC research is still relatively new, numerous studies have demonstrated their ability to improve nerve function and peripheral neuropathy symptoms in preclinical models [34], [35]. However,
more research is needed to ensure their safety and efficacy in clinical applications.

3.2.3. Adipose-Derived Stem Cells (ADSCs)

In murine nervous system ischemia models, ADSC-based therapies have been found to promote neurological recovery; this field of study is still highly active [36], [37]. A variety of supporting structures, including Schwann-like cells, which carry many of the hallmarks of mature peripheral nervous system (PNS) cells, can be formed from ADSCs through chemical or neurosphere-differentiation [38], [39]. These cells resemble mature SCs in terms of their morphological characteristics. There is skepticism in the literature regarding the functioning and security of these differentiated cells, and many researchers think that the toxicity of the chemical differentiation techniques is the primary cause of the in vitro morphological and cytological changes [40]. Damaged tissue can be repaired through the three processes of cell engraftment and differentiation, release of neurotrophic factors, and immunosuppression [41]. For the ADSCs to develop a cell niche and differentiate from mesodermal to ectodermal lineages, cell engraftment and differentiation are necessary. Cell engraftment occurs after these cells are injected into a host environment. The ADSCs secrete a variety of neurotrophic factors during various stages of tissue regeneration, including epidermal growth factor (EGF), TGF-1, VEGF, basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), insulin growth factor (IGF-1), and brain-derived neurotrophic factor (BDNF), which may also help the injured peripheral nerve heal [41]–[43].

3.2.4. Mesenchymal Stromal Cells

The multipotent cells known as mesenchymal stromal cells (MSCs) are often found in nearly all post-natal organs and tissues [44], including the umbilical cord [45], placenta [46], and dental pulp. All these cells have differentiation properties and are multipotent. MSCs are ideal candidates for treating DPN in the meantime. Several markers, including CD54/CD102, CD166, CD73, CD90, CD44, and CD105, are used to identify MSCs [47]. MSCs are mesodermal cells that can develop into adipose tissue, cartilage, and bone [48]. MSCs, however, cannot meet the definition of a stem cell; hence there is debate about whether they are actual stem cells or not. Human MSCs’ capacity for self-renewal has not yet been established, and their differentiation into cells of multiple lineages sets HSCs apart [59]. The capacity to undergo precise and extensive differentiation into a small population of multipotent HSCs, which are among the organs that contain HSCs. The functional maturity of a small population of multipotent HSCs, which can multiply through self-renewal and differentiation, is the process by which all blood cell lineages are created. It only takes a few HSCs to start the full hematopoietic process. Numerous studies have discovered that long-term hematopoietic stem cells (LT-HSC) quiescence and activation are regulated by the genetic and epigenetic regulation of key molecules as well as by microenvironmental factors [59]. The capacity to undergo precise and extensive differentiation into cells of multiple lineages sets HSCs apart from other mature cells and their capacity for self-renewal.

The ST-HSC HSC/progenitor cells in the PB are thought to be the best sources of curative cells in regenerative medicine since they may directly aid in the recovery of damaged tissues. The clinical data suggest that the implantation of hematopoietic mononuclear cell fractions is associated with improved motor nerve conduction velocity (MNCV) due to neurotrophic effects, treating DPN with a therapeutic agent with dual angioneurotrophic activity may be more effective. As a result of their paracrine features, which include both angiogenic and neurotrophic effects, endothelial progenitor cells (EPCs) can be an ideal candidate for treating DPN. Cell therapy may also have long-lasting benefits, unlike protein or gene therapy. In peripheral blood and bone marrow (BM), EPCs are conceivably the progenitors of endothelial cells and are involved in postnatal neovascularization. According to mounting data, EPCs may be useful in treating various cardiovascular illnesses. References [54]–[56] EPCs function in the vasculature by transdifferentiation [54] and paracrine actions [56]. EPCs release various biological substances, including VEGF, IGF-1, and fibroblast growth factor-2 (FGF-2), which enable paracrine actions. There are indications that BM-derived EPCs could successfully treat DN by directly enhancing cerebral neovascularization. For the first time, Jeong et al. discovered that intramuscularly injected EPCs particularly concentrate around the vasa nervorum, preferentially engraft into peripheral nerves, and boost the production of several angiogenic and neurotrophic factors [57].

3.2.6. Hematopoietic Stem Cells

One of the most important cell sources for treating regenerative illnesses is regarded as hematopoietic stem cells (HSCs). HSCs are multipotent primordial cells that can differentiate into any type of blood cell, including those with lymphoid and myeloid ancestry [58]. Peripheral blood (PB), bone marrow (BM), and umbilical cord blood (UCB) are among the organs that contain HSCs. The functional maturity of a small population of multipotent HSCs, which can multiply through self-renewal and differentiation, is the process by which all blood cell lineages are created.

3.3. Efficacy of Stem Cell-Based Therapies

There are two basic mechanisms by which nerve damage from stem cell transplantation can be repaired. One involves increasing the local expression of neurotrophic factors such as FGF, VEGF-A, and nerve growth factor (NGF), which promote the development of axons, remyelination, angiogenesis, and protection against apoptotic cell death through paracrine action [51]. They also secrete anti-inflammatory, antiapoptotic chemicals. Mechanical allodynia and thermal hyperalgesia in neuropathic mice were found to be diminished following the transplantation of MSCs in the cerebral ventricle by Siniscalco et al. [52]. In STZ (streptozotocin)-induced diabetic mice, MSCs also reduce blood sugar levels by regenerating pancreatic beta cells [53]. Nevertheless, Canada, New Zealand, and Japan are currently using MSCs to treat acute graft-versus-host disease.
factors, while the other involves engrafting and differentiating cells into the components of big tissues [61]. The local expression of neurotrophic factors can often be improved by stem cells. Together, stem cells may improve mechanical allodynia, hyperalgesia, intraepidermal nerve fiber density, sciatic nerve blood flow, motor, and sensory nerve conduction velocity (MNCV and SNCV), capillary density, and single neuron blood flow (SNBF). The release of neurotrophic factors by various stem cell populations shows that MSCs, regardless of their origin, can lessen and mitigate the detrimental effects on injured nerve fibers, hence enhancing the function of the wounded nerve [62]. Stem cells are excellent prospects for halting and possibly reversing the debilitating effects of DPN due to the production of important neurotrophic factors as well as stem cells’ neuroprotective and neuroregenerative activities.

According to a recent study, peripheral blood mononuclear cell implantation helped the sciatic nerve’s MNCV and partially restored blood flow in rats with DPN [63]. According to Kim et al. intramuscular transplantation of BM-MNCs increases the expression of several angiogenic and neurotrophic factors in the rat vasa nervorum, including VEGF, FGF-2, IGF-1, and NOS-3. It enhanced nerve conduction velocity and encouraged nerve vascularity as a result [64]. According to Shibata et al., transplanting BM-MNCs improves the transplantation of NCV, increases the density of tiny capillaries in the muscle, and improves sciatic nerve blood flow in 8-week-old diabetic rats caused by STZ [65].

According to Kondo et al., transplanting BM-MNCs produced from young rats improved DPN, whereas BM-MNCs from adult or diabetic rats failed to demonstrate any efficacy [66]. There appears to be a substantial constraint in employing MSCs for DPN therapy, despite the positive effects of MSC transplantation in experimental DN that have previously been demonstrated. A study revealed that after being injected into mice with DPN, BM-derived MSCs might have chromosomal aberrations and develop malignant tumours. The thorough monitoring of chromosomal status for MSC transplantation following in vitro expansion is described in this study [67].

The ability of pluripotent stem cells to create every form of bodily cell makes them the new hope for regenerative medicine. DPN may respond favorably to the neural crest-like cells (NCL) produced from iPSCs [68]. When NCL is transplanted into diabetic mice caused by STZ, angiogenesis develops. The angiogenic factor, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), NGF, and Neurotrophin-3, which are released by NCL, are responsible for this. According to Okawa et al., NCL from old mice was transplanted into 16-week-old STZ-induced mice. These transplanted cells produced growth factors such as NGF and Neurotrophin-3 after four weeks and then differentiated into vascular smooth muscle cells, which restores the nerve and vascular functions that had been damaged [69]. However, inhibitors such as the potential for tumour development, epigenetic memory, and novel characteristics acquired during remodelling are observed in iPSCs [70]. Pluripotent stem cell therapy could be an effective option for treating DPN in its advanced stages if these barriers can be overcome.

According to Naruse et al., endothelial cell differentiation in the hind limbs of STZ-induced diabetic nude rats was boosted by intramuscular injection of EPCs. Blood flow and sciatic nerve conduction velocity (NCV) improve [71]. However, this study was unable to identify the precise way EPCs improve vascular health. Recent research has not always supported the hypothesis that EPC differentiation is a key factor in neovascularization [72]. The majority of therapeutic effects, however, come through angiogenesis rather than endothelial differentiation; the evidence strongly shows that BM-derived EPCs participate in the development of blood vessels through vasculogenesis. According to Naruse et al., transplantation of EPCs derived from cord blood into the skeletal muscles of the hind limbs increased the differentiation of EPCs into endothelial cells in the soleus muscle, which results in an increase in sciatic motor nerve conduction velocity and sciatic nerve blood flow in a rat DPN model [71]. According to more recent research, EPCs do not differentiate into ECs [72], [73].

4. DISCUSSION

Stem cell therapy for diabetic peripheral neuropathy is expected to have a transformative influence in the future and provide patients with this crippling ailment with new hope (Table 1). Stem cell therapy demonstrates potential for treating the root causes of the condition, fostering nerve regeneration, and easing peripheral neuropathy symptoms.

The capacity for regeneration offered by stem cell therapy is one of its most significant advantages. The ability of stem cells to develop into multiple cell types, such as neurons and supporting cells, is essential for mending injured nerves. Encouraging nerve regeneration and returning to normal function is feasible by administering stem cells to the damaged areas. Patients with diabetic peripheral neuropathy have had encouraging improvements in nerve conduction, pain relief, and sensory function due to preclinical and early-phase clinical research.

Another element of stem cell therapy’s potential influence is how individually tailored it is. Since every patient has a unique illness, stem cell therapy can be customized to meet those demands. Stem cell therapy can deliver tailored treatment that enhances therapeutic outcomes by carefully selecting patients, considering factors including disease severity and duration, and tailoring treatment procedures to suit individual patients [84]. Moreover, as our understanding of stem cells and their mechanisms of action continues to advance, future research will likely identify additional potential benefits and applications for stem cell therapy in diabetic peripheral neuropathy. This may include optimizing the selection of stem cell sources, exploring innovative delivery methods, and leveraging advancements in tissue engineering to enhance the efficacy of stem cell treatments. Additionally, stem cell therapy has the potential to be combined with other innovative approaches in the field of regenerative medicine [85]. For example, combining stem cell therapy with gene editing techniques or bioengineering strategies may further
enhance the reparative and regenerative capabilities of stem cells in treating diabetic peripheral neuropathy.

Exosome and mRNA function in diabetic peripheral neuropathy is a newly discovered field of investigation that has great potential for elucidating disease pathophysiology and creating novel therapeutic strategies [86]. Small membranous vesicles called exosomes are released by cells and are involved in intercellular communication. They contain a variety of bioactive compounds, including messenger RNAs (mRNAs) and microRNAs, as well as proteins, lipids, and nucleic acids. These exosomes can transport miRNAs and mRNAs to destination cells, modifying their gene expression and aiding in the regeneration of damaged nerve tissue [87]. Exosomes have been identified to carry specific miRNAs that control neuroinflammation, oxidative stress, and apoptosis, three important processes associated with the onset and progression of diabetic peripheral neuropathy [88]. Thus, exosomes and mRNA also serve as valuable biomarkers for the diagnosis and prognosis of diabetic peripheral neuropathy. However, more research is needed to fully understand the mechanisms of action, identify specific therapeutic targets, and optimise delivery strategies to harness the full potential of exosomes and mRNA for the treatment of diabetic peripheral neuropathy.

The possibility of stem cell therapy for diabetic peripheral neuropathy still faces several obstacles. These difficulties include maximising stem cell source selection, determining the best treatment timing and dosage, addressing long-term safety issues, managing regulatory restrictions, and assuring general accessibility and affordability.

As a result, stem cell therapy’s eventual implications on diabetic peripheral neuropathy are quite promising. Through the promotion of nerve regeneration, symptom relief, and enhancement of patient quality of life, stem cell
therapy has the potential to transform the treatment of this crippling ailment with additional study and development. But to fully utilise stem cell therapy’s benefits in diabetic peripheral neuropathy, challenges must be overcome, and treatment methods must be improved. Secondly, a key factor in optimising stem cell therapy is the route of administration. Methods of targeted delivery such as intravenous infusion, local injection, or both may be considered. To ensure the stem cells reach the damaged nerves and have a therapeutic effect, the best method of administration must be identified.

Additionally, understanding the optimal timing, dosage, and source of stem cells is crucial. The progression of diabetic peripheral neuropathy can vary among individuals, and administering stem cells at the appropriate stage may enhance treatment effectiveness. Likewise, determining the ideal cell dosage is essential to achieve the desired therapeutic outcome and minimise potential risks. Besides, it is also crucial to customise the patient selection criteria to identify those with specific needs who will benefit from stem cell therapy the most. Patient selection should consider elements including disease severity, diabetes duration, and the existence of concomitant comorbidities. The therapy is targeted and can produce the best results thanks to this individualised approach.

The safety and effectiveness of stem cell therapy must also be assessed over an extended period with careful observation. Comprehensive evaluation methods, such as sensory and motor function tests, nerve conduction investigations, skin biopsy and patient-reported outcome measures, should be implemented to monitor the progress of treated patients over time.

### 5. Conclusion

This review aims to provide a comprehensive overview of the current understanding of stem cell therapy in managing peripheral diabetic neuropathy. By evaluating preclinical and clinical studies, exploring different sources of stem cells, and discussing potential optimisation strategies, this study contributes to the growing body of knowledge in the application of stem cell therapy for DPN. Apart from the possibility of using exosomes, the cocktail of bioactive mediators present in the conditioned medium of MSCs could convert a neurodestructive/pro-inflammatory microenvironment to a neuroprotective/anti-inflammatory one. Thus, using a conditioned medium of MSCs may be an excellent and novel therapeutic method to reverse the initial stages of DPN, avoiding the generation of foot ulcers and reducing the risk of lower limb amputation. Ultimately, affirming the potential of stem cell therapy as a transformative therapeutic approach for improving the quality of life for DPN patients, it is advised to employ this technique in a pilot clinical trial for those who are badly affected by DPN because numerous clinical trials have demonstrated the safety of autologous hematopoietic and mesenchymal stem cells. Axonal growth, immunomodulation, angiogenesis, remyelination, and protection from apoptotic cell death are supported by MSC therapies that target both vascular and neural elements, which are advantageous in treating DPN through the modification of the central nervous system-injured environment and promote repair.

Thus, stem cell therapy’s eventual implications on diabetic peripheral neuropathy are promising. Through the promotion of nerve regeneration, symptom relief, and enhancement of patient quality of life, stem cell therapy has the potential to transform the treatment of this crippling ailment with additional study and development. But to fully utilize stem cell therapy’s benefits in DPN, challenges must be overcome, and treatment methods must be improved.

### Author Contributions

Sanjay Sharma: Conceptualization (equal); Formal Analysis (equal); Resources (equal); Writing-review and editing (equal). Ravi Velamoor Rangarajan: Data curation (equal); Methodology (equal); Project administration (equal); Resources (equal); Writing-original draft (equal).

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### Conflict of Interest

Authors declare that they do not have any conflict of interest.

### Abbreviations

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<th>Abbreviation</th>
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<tr>
<td>DPN</td>
<td>Diabetic peripheral neuropathy</td>
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<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<td>IV</td>
<td>Intravenous</td>
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<td>FGF</td>
<td>Fibroblast growth factor</td>
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<td>ECM</td>
<td>Extracellular matrix</td>
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<td>PEDF</td>
<td>Pigment epithelium-derived factor</td>
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<td>LRP</td>
<td>Lipoprotein receptor-related protein</td>
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<td>TSP</td>
<td>Thrombospondin</td>
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<td>CXCL</td>
<td>Chemokine (C-X-C-motif) ligand</td>
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<td>CXCR</td>
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<td>(NG)2</td>
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<td>(RG)5</td>
<td>Regulator of G protein signaling 5</td>
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<td>BM-MSC</td>
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<td>Induced pluripotent stem cells</td>
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<td>Adipose-derived stem cells</td>
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<td>PNS</td>
<td>Peripheral nervous system</td>
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<td>Basic fibroblast growth factor</td>
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<td>Hepatocyte growth factor</td>
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<td>Insulin growth factor</td>
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<td>STZ</td>
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<td>DN</td>
<td>Diabetic neuropathy</td>
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REFERENCES


